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FILE 'HOME' ENTERED AT 10:22:01 ON 24 FEB 2003

=> file .nash
=> s spla2 and Ca? (2w) dependent
L1          24 FILE MEDLINE
L2          32 FILE CAPLUS
L3           4 FILE SCISEARCH
L4           1 FILE LIFESCI
L5          15 FILE BIOSIS
L6          19 FILE EMBASE

TOTAL FOR ALL FILES
L7          95 SPLA2 AND CA? (2W) DEPENDENT

=> s l7 not 2001-2003/py
TOTAL FOR ALL FILES
L14         77 L7 NOT 2001-2003/PY

=> dup rem l14
PROCESSING COMPLETED FOR L14
L15         30 DUP REM L14 (47 DUPLICATES REMOVED)

=> d ibib abs 1-30

L15  ANSWER 1 OF 30  CAPLUS  COPYRIGHT 2003 ACS        DUPLICATE 1
ACCESSION NUMBER:        2001:15304  CAPLUS
DOCUMENT NUMBER:         134:218734
TITLE:                   Cloning and recombinant expression of a structurally
                         novel human secreted phospholipase A2
AUTHOR(S):               Gelb, Michael H.; Valentin, Emmanuel; Ghomashchi,
                         Farideh; Lazdunski, Michel; Lambeau, Gerard
CORPORATE SOURCE:        Departments of Chemistry and Biochemistry, University
                         of Washington, Seattle, WA, 98195, USA
SOURCE:                  Journal of Biological Chemistry (2000), 275(51),
                         39823-39826
                         CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER:               American Society for Biochemistry and Molecular
                         Biology
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Mammals contain a diverse set of secreted phospholipases A2 (sPLA2s) that
     liberate arachidonic acid from phospholipids for the prodn. of eicosanoids
     and exert a variety of physiol. and pathol. effects.  We report the
     cloning, recombinant expression, and kinetic properties of a novel human
     sPLA2 that defines a new structural class of sPLA2s called group
     XII.  The human group XII (hGXII) cDNA contains a putative signal peptide
     of 22 residues followed by a mature protein of 167 amino acids that
     displays homol. to all known sPLA2s only over a short stretch of amino
     acids in the active site region.  Northern blot and reverse
     transcription-polymerase chain reaction analyses show that the tissue
     distribution of hGXII is distinct from the other human sPLA2s with strong
     expression in heart, skeletal muscle, kidney, and pancreas and weaker
     expression in brain, liver, small intestine, lung, placenta, ovaries,
     testis, and prostate.  Catalytically active hGXII was produced in
     Escherichia coli and shown to be Ca2+-dependent
     despite the fact that it is predicted to have an unusual Ca2+-binding
     loop.  Similar to the previously characterized mouse group IIE sPLA2s, the
     specific activity of hGXII is low in comparison to that of other mammalian
     sPLA2, suggesting that hGXII could have novel functions that are
     independent of its phospholipase A2 activity.
REFERENCE COUNT:         37    THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15  ANSWER 2 OF 30  CAPLUS  COPYRIGHT 2003 ACS        DUPLICATE 2
ACCESSION NUMBER:        2000:208591  CAPLUS
DOCUMENT NUMBER:         133:1934
TITLE:                   Novel human secreted phospholipase A2 with homology to
                         the group III bee venom enzyme
AUTHOR(S):               Valentin, Emmanuel; Ghomashchi, Farideh; Gelb, Michael
```

H.; Lazdunski, Michel; Lambeau, Gerard
CORPORATE SOURCE: Institut de Pharmacologie Moleculaire et Cellulaire, CNRS-UPR 411, Valbonne, 06560, Fr.
SOURCE: Journal of Biological Chemistry (2000), 275(11), 7492-7496
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Venom and mammalian secreted phospholipases A2 (sPLA2s) have been assocd. with numerous physiol., pathol., and toxic processes. So far, structurally related group I and II sPLA2s have been found in vertebrates such as mammals and snakes, whereas group III sPLA2s have mainly been found in venom from invertebrates such as bees and scorpions. Here we report the cloning and expression of a cDNA coding for a human group III (hGIII) **sPLA2**. The full-length cDNA codes for a signal peptide of 19 residues followed by a protein of 490 amino acids made up of a central **sPLA2** domain (141 residues) flanked by large N- and C-terminal regions (130 and 219 residues, resp.). The **sPLA2** domain is 31% identical to bee venom **sPLA2** and displays all of the features of group III sPLA2s including 10 cysteines. The hGIII **sPLA2** gene consists of at least 7 exons and maps to chromosome 22q. By Northern blot anal., a 4.4-kilobase hGIII transcript was found in kidney, heart, liver, and skeletal muscle. Transfection of hGIII **sPLA2** cDNA in COS cells led to accumulation of **sPLA2** activity in the culture medium, indicating that the cDNA codes for a secreted enzyme. Using small unilamellar vesicles as substrate, hGIII **sPLA2** was found to be a **Ca2+-dependent** enzyme showing an 11-fold preference for phosphatidylglycerol over phosphatidylcholine and optimal activity at pH 8.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 30 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000243597 MEDLINE
DOCUMENT NUMBER: 20243597 PubMed ID: 10779801
TITLE: Secretory phospholipases A2 induce beta-glucuronidase release and IL-6 production from human lung macrophages.
AUTHOR: Triggiani M; Granata F; Oriente A; De Marino V; Gentile M; Calabrese C; Palumbo C; Marone G
CORPORATE SOURCE: Division of Clinical Immunology and Allergy, University of Naples Federico II, Naples, Italy.. triggian@unina.it
SOURCE: JOURNAL OF IMMUNOLOGY, (2000 May 1) 164 (9) 4908-15.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000606
Last Updated on STN: 20000606
Entered Medline: 20000522

AB Secretory phospholipases A2 (sPLA2s) are a group of extracellular enzymes that release fatty acids at the sn-2 position of phospholipids. Group IIA **sPLA2** has been detected in inflammatory fluids, and its plasma level is increased in inflammatory diseases. To investigate a potential mechanism of **sPLA2**-induced inflammation we studied the effect of group IA (from cobra venom) and group IIA (human synovial) sPLA2s on human macrophages. Both sPLA2s induced a concentration- and **Ca2+-dependent**, noncytotoxic release of beta-glucuronidase (16.2 +/- 2.4% and 13.1 +/- 1.5% of the total content with groups IA and IIA, respectively). Both sPLA2s also increased the rate of secretion of IL-6 and enhanced the expression of IL-6 mRNA. Preincubation of macrophages with inhibitors of the hydrolytic activity of **sPLA2** or cytosolic PLA2 did not influence the release of beta-glucuronidase. Incubation of macrophages with p-aminophenyl-mannopyranoside-BSA (mp-BSA), a ligand of the mannose receptor, also resulted in beta-glucuronidase release. However, while preincubation of macrophages with mp-BSA had no effect on beta-glucuronidase release induced by group IIA **sPLA2**, it enhanced that induced by group IA **sPLA2**. A blocking Ab

anti-mannose receptor inhibited both mp-BSA- and group IIA-induced beta-glucuronidase release. Taken together, these data indicate that group IA and IIA sPLA2s activate macrophages with a mechanism independent from their enzymatic activities and probably related to the activation of the mannose receptor or **sPLA2**-specific receptors. The secretion of enzymes and cytokines induced by sPLA2s from human macrophages may play an important role in inflammation and tissue damage associated with the release of sPLA2s.

L15 ANSWER 4 OF 30 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 4
ACCESSION NUMBER: 2000:466861 CAPLUS
DOCUMENT NUMBER: 133:160159
TITLE: Pyrimidinoceptor potentiation of macrophage PGE2 release involved in the induction of nitric oxide synthase
AUTHOR(S): Chen, Bing-C.; Lin, Wan-W.
CORPORATE SOURCE: Department of Pharmacology, College of Medicine, National Taiwan University, Taipei, Taiwan
SOURCE: British Journal of Pharmacology (2000), 130(4), 777-786
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have previously demonstrated that **Ca2+/calmodulin-dependent** protein kinase (CaMK) mediates pyrimidinoceptor potentiation of LPS-elicited inducible nitric oxide synthase (iNOS) induction in murine J774 macrophages. In the present paper, the authors have explored the role of cyclooxygenase (COX)-dependent prostaglandin E2 (PGE2) formation in this event. In J774 macrophages predominantly expressing P2Y6 receptors, the simultaneous addn. of UTP and lipopolysaccharide (LPS) resulted in potentiated increase in PGE2 release. UTP-induced increased PGE2 release was demonstrated by a concomitant increase in COX-2 protein expression, and was decreased by inhibitors specific for phosphatidylinositide-phospholipase C (PI-PLC), CaMK, protein kinase C (PKC), nuclear factor-kappa B (NF-.kappa.B) or COX-2. NS-398 (a selective COX-2 inhibitor) reduced LPS plus UTP-elicited iNOS induction and nitrite accumulation, supporting for the pos. regulation of iNOS gene expression by endogenous PGE2. Moreover, the **cAMP**/PKA-**dependent** up-regulation of iNOS expression mediated by PGE2 was drawn from the inhibitory effects of 2',5'-dideoxyadenosine, KT5720 and H-89. Exogenous PGE2 induced NF-.kappa.B activation and potentiated nitrite accumulation in response to LPS. In addn. to COX-2 induction, arachidonic acid (AA) release and steady-state mRNA levels of type V secretory phospholipase A2 (**sPLA2**) and Ca2+-independent PLA2 (iPLA2) were also increased in the presence of LPS and UTP; the LPS-induced increase in iPLA2 activity was also potentiated by UTP. Taken together, the authors conclude that UTP-mediated COX-2 and iPLA2 potentiation and PGE2 formation contribute to the iNOS induction, and that CaMK activation is the primary step in the UTP enhancement of COX-2 induction.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 5 OF 30 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2001181519 MEDLINE
DOCUMENT NUMBER: 21118648 PubMed ID: 11227220
TITLE: Activities and interactions among phospholipases A2 during thapsigargin-induced S49 cell death.
AUTHOR: Wilson H A; Allred D V; O'Neill K; Bell J D
CORPORATE SOURCE: Department of Zoology, Brigham, Young University, Provo, Utah 84602, USA.
SOURCE: APOPTOSIS, (2000 Oct) 5 (4) 389-96.
Journal code: 9712129. ISSN: 1360-8185.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404

Entered Medline: 20010329

AB The purpose of this study was to determine the roles of **calcium-dependent** phospholipase A2 (cPLA2) and calcium-independent phospholipase A2 (iPLA2) in thapsigargin-induced membrane susceptibility to secretory phospholipase A2 (**sPLA2**) and programmed cell death. 3H-arachidonic acid release was observed in the presence of thapsigargin. This release was inhibited partially by an inhibitor of iPLA2 (BEL) and completely by an inhibitor of both cPLA2 and iPLA2 (MAFP) suggesting that these enzymes were active during apoptosis. The process of cell death did not require the activity of either enzyme since neither inhibitor impeded the progression of apoptosis. However, both inhibitors increased the susceptibility of the membrane to **sPLA2** in the presence of thapsigargin. In the case of BEL, this effect appeared to involve direct induction of apoptosis in a sub-population of the cells independent of the action of iPLA2. In conclusion, the results suggested that cPLA2 and iPLA2 are active during thapsigargin-induced apoptosis in S49 cells and that cPLA2 tempers the tendency of the cells to become susceptible to **sPLA2** during apoptosis.

L15 ANSWER 6 OF 30 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 6
ACCESSION NUMBER: 2000:855358 CAPLUS
DOCUMENT NUMBER: 134:174772
TITLE: Cloning and Recombinant Expression of Human Group IIF-Secreted Phospholipase A2
AUTHOR(S): Valentin, Emmanuel; Singer, Alan G.; Ghomashchi, Farideh; Lazdunski, Michel; Gelb, Michael H.; Lambeau, Gerard
CORPORATE SOURCE: CNRS-UPR 411, Institut de Pharmacologie Moleculaire et Cellulaire, Sophia Antipolis, Valbonne, 06560, Fr.
SOURCE: Biochemical and Biophysical Research Communications (2000), 279, 223-228
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mammalian-secreted phospholipases A2 (**sPLA2**) form a diverse family of at least nine enzymes that hydrolyze phospholipids to release free fatty acids and lysophospholipids. We report here the cloning and characterization of human group IIF **sPLA2** (hGIIF **sPLA2**). The full-length cDNA codes for a signal peptide of 20 amino acid followed by a mature protein of 148 amino acids contg. all of the structural features of catalytically active group II sPLA2s. The hGIIF **sPLA2** gene is located on chromosome 1 and lies within a **sPLA2** gene cluster of about 300 kbp that also contains the genes for group IIA, IIC, IID, IIE, and V sPLA2s. In adult tissues, hGIIF is highly expressed in placenta, testis, thymus, liver, and kidney. Finally, recombinant expression of hGIIF **sPLA2** in Escherichia coli shows that the enzyme is **Ca2+-dependent**, maximally active at pH 7-8, and hydrolyzes phosphatidylglycerol vs. phosphatidylcholine with a 15-fold preference. (c) 2000 Academic Press.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 7 OF 30 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:291813 CAPLUS
DOCUMENT NUMBER: 133:206010
TITLE: Signal transduction in esophageal and LES circular muscle contraction
AUTHOR(S): Harnett, Karen M.; Cao, Weibiao; Kim, Nayoung; Sohn, Uy Dong; Rich, Harlan; Behar, Jose; Biancani, Piero
CORPORATE SOURCE: Department of Medicine, Rhode Island Hospital and Brown University, Providence, RI, USA
SOURCE: Yale Journal of Biology and Medicine (2000), Volume Date 1999, 72(2/3), 153-168
CODEN: YJBMAU; ISSN: 0044-0086
PUBLISHER: Yale Journal of Biology and Medicine
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 81 refs. Contraction of normal esophageal circular muscle (ESO) in response to acetylcholine (ACh) is linked to M2 muscarinic receptors activating at least three intracellular phospholipases, i.e.,

phosphatidylcholine-specific phospholipase C (PC-PLC), phospholipase D (PLD), and the high-mol.-wt. (85 kDa) cytosolic phospholipase A2 (cPLA2) to induce phosphatidylcholine (PC) metab., prodn. of diacylglycerol (DAG) and arachidonic acid (AA), resulting in activation of a protein kinase C (PKC)-dependent pathway. In contrast, lower esophageal sphincter (LES) contraction induced by maximally EDs of ACh is mediated by muscarinic M3 receptors, linked to pertussis toxin-insensitive GTP-binding proteins of the Gq/11 type. They activate phospholipase C, which hydrolyzes phosphatidylinositol bis-phosphate (PIP2), producing inositol 1,4,5-trisphosphate (IP3) and DAG. IP3 causes release of intracellular Ca2+ and formation of a Ca2+-calmodulin complex, resulting in activation of myosin light-chain kinase and contraction through a **calmodulin -dependent** pathway. Signal transduction pathways responsible for maintenance of LES tone are quite distinct from those activated during contraction in response to maximally EDs of agonists, e.g., ACh. Resting LES tone is assocd. with activity of a low-mol.-wt. (.apprx.14 kDa) pancreatic-like (group I) secreted phospholipase A2 (**sPLA2**) and prodn. of arachidonic acid (AA), which is metabolized to prostaglandins and thromboxanes. These AA metabolites act on receptors linked to G-proteins to induce activation of PI- and PC-specific phospholipases, and prodn. of second messengers. Resting LES tone is assocd. with submaximal PI hydrolysis resulting in submaximal levels of inositol trisphosphate (IP3)-induced Ca2+ release, and interaction with DAG to activate PKC. In an animal model of acute esophagitis, acid-induced inflammation alters the contractile pathway of ESO and LES. In LES circular muscle, after induction of exptl. esophagitis, basal levels of PI hydrolysis are substantially reduced and intracellular Ca++ stores are functionally damaged, resulting in a redn. of resting tone. The redn. in intracellular Ca2+ release causes a switch in the signal transduction pathway mediating contraction in response to ACh. In the normal LES, ACh causes release of Ca2+ from intracellular stores and activation of a **calmodulin-dependent** pathway. After esophagitis, ACh-induced contraction depends on influx of extracellular Ca2+, which is insufficient to activate calmodulin, and contraction is mediated by a PKC-dependent pathway. These changes are reproduced in normal LES cells by thapsigargin-induced depletion of Ca2+ stores, suggesting that the amt. of Ca2+ available for release from intracellular stores defines the signal transduction pathway activated by a maximally ED of ACh.

REFERENCE COUNT: 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 8 OF 30 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 7

ACCESSION NUMBER: 2000:2092 CAPLUS
DOCUMENT NUMBER: 132:136252
TITLE: Specificity of endogenous fatty acid release during tumor necrosis factor-induced apoptosis in WEHI 164 fibrosarcoma cells
AUTHOR(S): Brekke, Ole-L.; Sagen, Erling; Bjerve, Kristian S.
CORPORATE SOURCE: Department of Clinical Chemistry, University Hospital, Norwegian University of Science and Technology, Trondheim, N-7006, Norway
SOURCE: Journal of Lipid Research (1999), 40(12), 2223-2233
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: Lipid Research, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recombinant tumor necrosis factor alpha (rTNF-.alpha.)-induced release of endogenous fatty acids was examd. in WEHI 164 clone 13 fibrosarcoma cells using a highly sensitive HPLC method. The initial rTNF-.alpha.-induced extracellular release of endogenous fatty acids was dominated by 20:4n-6, 22:4n-6, 24:4n-6, and 18:1n-9 showing relative rates of 2.9, 0.9, 1.1, and 1.0, resp. Release of endogenous AA and DNA fragmentation occurred simultaneously and preceded cell death by approx. 2 h. Me arachidonoyl fluorophosphonate and LY 311727, specific inhibitors of **Ca2+-dependent** cytosolic PLA2 (cPLA2) and secretory PLA2 (**sPLA2**), resp., neither blocked rTNF-.alpha.-induced cytotoxicity or endogenous AA release. However, both inhibitors reduced rTNF-.alpha.-induced release of other endogenous fatty acids. In comparison, the antioxidant butylated hydroxyanisole (BHA) completely inhibited the rTNF-.alpha.-induced cytotoxicity as well as AA release mediated through the TNF receptor p55, while the very similar antioxidant butylated hydroxytoluene had no effect.

BHA did not inhibit recombinant cPLA2 or **sPLA2** enzyme activity in vitro. Furthermore, stimulation of cells with rTNF-.alpha. for 4 h did not increase cPLA2 enzyme activity. The data indicate that neither cPLA2 or **sPLA2** mediate rTNF-.alpha.-induced apoptosis and extracellular AA release in WEHI cells. The results suggest that a BHA-sensitive signaling pathway coupled to AA release is a key event in TNF-induced cytotoxicity in these cells.

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 9 OF 30 MEDLINE

ACCESSION NUMBER: 2000131981 MEDLINE
DOCUMENT NUMBER: 20131981 PubMed ID: 10667329
TITLE: Role of type IIA secretory phospholipase A2 in arachidonic acid metabolism.
AUTHOR: Kuwata H; Sawada H; Murakami M; Kudo I
CORPORATE SOURCE: Department of Health Chemistry, School of Pharmaceutical Sciences, Showa University, Tokyo, Japan.
SOURCE: ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1999) 469 183-8.
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000323

AB Recent recognition of the rapidly growing **sPLA2** family has led to a suggestion that some of the previously described functions of **sPLA2**-IIA need to be reevaluated, since studies based upon enzyme activities and using inhibitors or antibodies against **sPLA2**-IIA may not discriminate these sPLA2s. Our present studies reconfirm the involvement of **sPLA2**-IIA in biological responses, demonstrated significant crosstalk between the two **Ca**(2+)-**dependent** PLA2s (cPLA2 and **sPLA2**) where one enzyme is required for the induction of the other, and revealed segregated coupling of discrete PLA2 and COX enzymes in the different phases of PG biosynthesis. Based upon the analysis of cells derived from **sPLA2**-IIA "natural knock-out" mice, it is apparent that **sPLA2**-IIA is not essential for the initiation of delayed PGE2 biosynthesis. However, it is capable of contributing to the delayed response as an enhancer when appropriately induced by proinflammatory stimuli, leading to optimal COX-2-dependent PGE2 generation. Importantly, in order for **sPLA2**-IIA (or related **sPLA2** isozymes) to attack the biological membranes, so-called "membrane rearrangement" should take place in activated, but not resting, cells. Membrane rearrangement also occurs when cells are undergoing apoptosis, during which acidic phospholipids, the preferred substrates for **sPLA2**-IIA, are exposed on the outer leaflet of the plasma membranes. Nonetheless, in view of the dramatically elevated levels of **sPLA2**-IIA in inflamed or ischemic sites, it is likely that this extracellular isozyme participates in the expansion of chronic tissue disorders by augmenting generation of proinflammatory eicosanoids or lysophospholipids, depending upon the states of the inflammatory response.

L15 ANSWER 10 OF 30 MEDLINE DUPLICATE 8

ACCESSION NUMBER: 2000241489 MEDLINE
DOCUMENT NUMBER: 20241489 PubMed ID: 10780577
TITLE: Signal transduction in esophageal and LES circular muscle contraction.
AUTHOR: Harnett K M; Cao W; Kim N; Sohn U D; Rich H; Behar J; Biancani P
CORPORATE SOURCE: Department of Medicine, Rhode Island Hospital and Brown University, Providence 02903, USA.
CONTRACT NUMBER: DK-28614 (NIDDK)
SOURCE: YALE JOURNAL OF BIOLOGY AND MEDICINE, (1999 Mar-Jun) 72 (2-3) 153-68. Ref: 81
Journal code: 0417414. ISSN: 0044-0086.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000525
Last Updated on STN: 20000525
Entered Medline: 20000516

AB Contraction of normal esophageal circular muscle (ESO) in response to acetylcholine (ACh) is linked to M2 muscarinic receptors activating at least three intracellular phospholipases, i.e., phosphatidylcholine-specific phospholipase C (PC-PLC), phospholipase D (PLD), and the high molecular weight (85 kDa) cytosolic phospholipase A2 (cPLA2) to induce phosphatidylcholine (PC) metabolism, production of diacylglycerol (DAG) and arachidonic acid (AA), resulting in activation of a protein kinase C (PKC)-dependent pathway. In contrast, lower esophageal sphincter (LES) contraction induced by maximally effective doses of ACh is mediated by muscarinic M3 receptors, linked to pertussis toxin-insensitive GTP-binding proteins of the G(q/11) type. They activate phospholipase C, which hydrolyzes phosphatidylinositol bisphosphate (PIP2), producing inositol 1,4,5-trisphosphate (IP3) and DAG. IP3 causes release of intracellular Ca++ and formation of a Ca++-calmodulin complex, resulting in activation of myosin light chain kinase and contraction through a **calmodulin -dependent** pathway. Signal transduction pathways responsible for maintenance of LES tone are quite distinct from those activated during contraction in response to maximally effective doses of agonists (e.g., ACh). Resting LES tone is associated with activity of a low molecular weight (approximately 14 kDa) pancreatic-like (group 1) secreted phospholipase A2 (**sPLA2**) and production of arachidonic acid (AA), which is metabolized to prostaglandins and thromboxanes. These AA metabolites act on receptors linked to G-proteins to induce activation of PI- and PC-specific phospholipases, and production of second messengers. Resting LES tone is associated with submaximal PI hydrolysis resulting in submaximal levels of inositol trisphosphate (IP3-induced Ca++ release, and interaction with DAG to activate PKC. In an animal model of acute esophagitis, acid-induced inflammation alters the contractile pathway of ESO and LES. In LES circular muscle, after induction of experimental esophagitis, basal levels of PI hydrolysis are substantially reduced and intracellular Ca++ stores are functionally damaged, resulting in a reduction of resting tone. The reduction in intracellular Ca++ release causes a switch in the signal transduction pathway mediating contraction in response to ACh. In the normal LES, ACh causes release of Ca++ from intracellular stores and activation of a **calmodulin-dependent** pathway. After esophagitis, ACh-induced contraction depends on influx of extracellular Ca++, which is insufficient to activate calmodulin, and contraction is mediated by a PKC-dependent pathway. These changes are reproduced in normal LES cells by thapsigargin-induced depletion of Ca++ stores, suggesting that the amount of Ca++ available for release from intracellular stores defines the signal transduction pathway activated by a maximally effective dose of ACh.

L15 ANSWER 11 OF 30 MEDLINE
ACCESSION NUMBER: 1999310576 MEDLINE
DOCUMENT NUMBER: 99310576 PubMed ID: 10381350
TITLE: Secretory phospholipase A2 induces phospholipase Cgamma-1 activation and Ca2+ mobilization in the human astrocytoma cell line 1321N1 by a mechanism independent of its catalytic activity.
AUTHOR: Hernandez M; Barrero M J; Alvarez J; Montero M; Sanchez Crespo M; Nieto M L
CORPORATE SOURCE: Instituto de Biologia y Genetica Molecular, Facultad de Medicina, Consejo Superior de Investigaciones Cientificas and Universidad de Valladolid, Valladolid, 47005-, Spain.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1999 Jun 24) 260 (1) 99-104.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199907

ENTRY DATE: Entered STN: 19990806
Last Updated on STN: 20021218
Entered Medline: 19990729

AB The effect of secretory phospholipase A2 (**sPLA2**) on intracellular Ca2+ signaling in human astrocytoma cells was studied. **sPLA2** increased cytosolic [Ca2+] ([Ca2+]c) in both Ca2+-containing and Ca2+-free medium, thus suggesting Ca2+ release from intracellular stores. The activation by **sPLA2** of arachidonate release via cytosolic PLA2 (cPLA2) was also independent of extracellular Ca2+. As **sPLA2** requires Ca2+ for activity, these results indicate that both Ca2+ mobilization and cPLA2 activation induced by **sPLA2** are unrelated to phospholipase activity but dependent on signaling mechanisms. The **sPLA2**-induced [Ca2+]c peak was sensitive to Bordetella pertussis toxin and inhibited by caffeine, suggesting its mediation by inositol 1,4,5-trisphosphate (IP3). **sPLA2** induced tyrosine phosphorylation and membrane targeting of phospholipase Cgamma-1 (PLCgamma-1). Moreover, the Ca2+ peak was sensitive to protein tyrosine kinase inhibitors. **sPLA2** activates two signaling pathways: one leading to the activation of the MAP kinase/cPLA2 cascade and another leading to PLCgamma activation and Ca2+ release.

L15 ANSWER 12 OF 30 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 1999296146 MEDLINE
DOCUMENT NUMBER: 99296146 PubMed ID: 10369455
TITLE: Cross-talk between group IIA-phospholipase A2 and inducible NO-synthase in rat renal mesangial cells.
AUTHOR: Rupprecht G; Scholz K; Beck K F; Geiger H; Pfeilschifter J; Kaszkin M
CORPORATE SOURCE: Klinikum der Johann-Wolfgang-Goethe-Universitat, Medizinische Klink IV, Funktionsbereich Nephrologie, Frankfurt am Main, Germany.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1999 May) 127 (1) 51-6. Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990913
Last Updated on STN: 19990913
Entered Medline: 19990901

AB Features of glomerulonephritis are expression of the inducible form of NO synthase (iNOS) as well as expression of the secretory group IIA-phospholipase A2 (**sPLA2**) in mesangial cells. Interleukin 1beta (IL-1beta) induces both enzymes with a similar time course resulting in an increase in nitrite production and **sPLA2**-IIA activity. In this study we investigated the relationship between the formation of NO and **sPLA2**-IIA induction in rat renal mesangial cells. Incubation of mesangial cells with the NO-donor, spermine-NONOate, for 24 h induced **sPLA2**-IIA mRNA expression and activity, whereas S-nitroso glutathione alone had only a small stimulatory effect. Stimulation of cells with IL-1beta caused a marked increase in **sPLA2**-IIA mRNA and activity that were potentiated 3 fold by both NO donors. Coincubation of cells with IL-1beta and the NOS inhibitor, L-N(G) monomethylarginine (L-NMMA), **caused** a dose-**dependent** inhibition of cytokine-induced **sPLA2**-IIA mRNA expression and activity. **sPLA2**-IIA activity was not stimulated by 8-bromo-cyclic GMP indicating that NO-induced **sPLA2**-IIA induction is independent of cyclic GMP-mediated signal transduction. These data show that NO contributes to the expression by cytokines of **sPLA2**-IIA and establishes a novel type of interaction between iNOS and **sPLA2** -IIA in mesangial cells. This cross-talk between inflammatory mediators may help to promote and sustain an inflammatory state in the kidney.

L15 ANSWER 13 OF 30 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 1998218829 MEDLINE
DOCUMENT NUMBER: 98218829 PubMed ID: 9559902
TITLE: Pharmacological comparison of UTP- and thapsigargin-induced arachidonic acid release in mouse RAW 264.7 macrophages.
AUTHOR: Lin W W; Chen B C

CORPORATE SOURCE: Department of Pharmacology, College of Medicine, National Taiwan University, Taipei.
SOURCE: BRITISH JOURNAL OF PHARMACOLOGY, (1998 Mar) 123 (6) 1173-81.
Journal code: 7502536. ISSN: 0007-1188.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980609
Last Updated on STN: 19980609
Entered Medline: 19980528

AB 1. Although stimulation of mouse RAW 264.7 macrophages by UTP elicits a rapid increase in intracellular free Ca2+ ([Ca2+]i), phosphoinositide (PI) turnover, and arachidonic acid (AA) release, the causal relationship between these signalling pathways is still unclear. In the present study, we investigated the involvement of phosphoinositide-dependent phospholipase C (PI-PLC) activation, Ca2+ increase and protein kinase activation in UTP-induced AA release. The effects of stimulating RAW 264.7 cells with thapsigargin, which cannot activate the inositol phosphate (IP) cascade, but results in the release of sequestered Ca2+ and an influx of extracellular Ca2+, was compared with the effects of UTP stimulation to elucidate the multiple regulatory pathways for cPLA2 activation. 2. In RAW 264.7 cells UTP (100 microM) and thapsigargin (1 microM) caused 2 and 1.2 fold increases, respectively, in [3H]-AA release. The release of [3H]-AA following treatment with UTP and thapsigargin were non-additive, totally abolished in the Ca2+-free buffer, BAPTA (30 microM)-containing buffer or in the presence of the cPLA2 inhibitor MAFP (50 microM), and inhibited by pretreatment of cells with pertussis toxin (100 ng ml(-1)) or 4-bromophenacyl bromide (100 microM). By contrast, aristolochic acid (an inhibitor of **sPLA2**) had no effect on UTP and thapsigargin responses. 3. U73122 (10 microM) and neomycin (3 mM), inhibitors of PI-PLC, inhibited UTP-induced IP formation (88% and 83% inhibition, respectively) and AA release (76% and 58%, respectively), accompanied by a decrease in the [Ca2+]i rise. 4. Wortmannin attenuated the IP response of UTP in a concentration-dependent manner (over the range 10 nM-3 microM), and reduced the UTP-induced AA release in parallel. RHC 80267 (30 microM), a specific diacylglycerol lipase inhibitor, had no effect on UTP-induced AA release. 5. Short-term treatment with PMA (1 microM) inhibited the UTP-stimulated accumulation of IP and increase in [Ca2+]i, but had no effect on the release of AA. In contrast, the AA release caused by thapsigargin was increased by PMA. 6. The role of PKC in UTP- and thapsigargin-mediated AA release was shown by the blockade of these effects by staurosporine (1 microM), Ro 31-8220 (10 microM), Go 6976 (1 microM) and the down-regulation of PKC. 7. Following treatment of cells with SK&F 96365 (30 microM), thapsigargin-, but not UTP-, induced Ca2+ influx, and the accompanying AA release, were down-regulated. 8. Neither PD 98059 (100 microM), MEK a inhibitor, nor genistein (100 microM), a tyrosine kinase inhibitor, had any effect on the AA responses induced by UTP and thapsigargin. 9. We conclude that UTP-induced cPLA2 activity depends on the activation of PI-PLC and the sustained elevation of intracellular Ca2+, which is essential for the activation of cPLA2 by UTP and thapsigargin. The [**Ca2**+]i-**dependent** AA release that follows treatment with both stimuli was potentiated by the activity of protein kinase C (PKC). A pertussis toxin-sensitive pathway downstream of the increase in [Ca2+]i was also shown to be involved in AA release.

L15 ANSWER 14 OF 30 MEDLINE
ACCESSION NUMBER: 1998079102 MEDLINE
DOCUMENT NUMBER: 98079102 PubMed ID: 9417122
TITLE: Secretory phospholipase A2 activates the cascade of mitogen-activated protein kinases and cytosolic phospholipase A2 in the human astrocytoma cell line 1321N1.
AUTHOR: Hernandez M; Burillo S L; Crespo M S; Nieto M L
CORPORATE SOURCE: Instituto de Biologia y Genetica Molecular, Universidad de Valladolid-Consejo Superior de Investigaciones Cientificas, 47005 Valladolid, Spain.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Jan 2) 273 (1) 606-12.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980217
Last Updated on STN: 19980217
Entered Medline: 19980203

AB The biological effects of type IIA 14-kDa phospholipase A2 (**sPLA2**) on 1321N1 astrocytoma cells were studied. **sPLA2** induced a release of [3H]arachidonic acid ([3H]AA) similar to that elicited by lysophosphatidic acid (LPA), a messenger acting via a G-protein-coupled receptor and a product of **sPLA2** on lipid microvesicles. In contrast, no release of [1-14C]oleate could be detected in cells labeled with this fatty acid. As these findings pointed to a selective mechanism of [3H]AA release, it was hypothesized that **sPLA2** could act by a signaling mechanism involving the activation of cytosolic PLA2 (cPLA2), i.e. the type of PLA2 involved in the release of [3H]AA elicited by agonists. In keeping with this view, stimulation of 1321N1 cells with **sPLA2** elicited the decrease in electrophoretic mobility that is characteristic of the phosphorylation of cPLA2, as well as activation of p42 mitogen-activated protein (MAP) kinase, c-Jun kinase, and p38 MAP kinase. Incubation with **sPLA2** of quiescent 1321N1 cells elicited a mitogenic response as judged from an increased incorporation of [3H]thymidine. Attempts to correlate the effect of extracellular PLA2 with the generation of LPA were negative. Incubation with pertussis toxin prior to the addition of either **sPLA2** or LPA only showed abrogation of the response to LPA, thus suggesting the involvement of pertussis-sensitive Gi-proteins in the case of LPA. Treatments with inhibitors of the catalytic effect of **sPLA2** such as p-bromophenacyl bromide and dithiothreitol did not prevent the effect on cPLA2 activation. In contrast, preincubation of 1321N1 cells with the antagonist of the **sPLA2** receptor p-aminophenyl-alpha-D-mannopyranoside-bovine serum albumin, blocked cPLA2 activation with a EC50 similar to that described for the inhibition of binding of **sPLA2** to its receptor. Moreover, treatment of 1321N1 cells with the MAP kinase kinase inhibitor PD-98059 inhibited the activation of both cPLA2 and p42 MAP kinase produced by **sPLA2**. In summary, these data indicate the existence in astrocytoma cells of a signaling pathway triggered by engagement of a **sPLA2**-binding structure, that produces the release of [3H]AA by activating the MAP kinase cascade and cPLA2, and leads to a mitogenic response after longer periods of incubation.

L15 ANSWER 15 OF 30 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 1998173797 MEDLINE
DOCUMENT NUMBER: 98173797 PubMed ID: 9512652
TITLE: Secretory and cytosolic phospholipases A2 are activated during TNF priming of human neutrophils.
AUTHOR: Seeds M C; Jones D F; Chilton F H; Bass D A
CORPORATE SOURCE: Department of Internal Medicine, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina 27157-1054, USA.. mseeds@bgsm.edu
CONTRACT NUMBER: PO1-HL50395 (NHLBI)
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1998 Jan 23) 1389 (3) 273-84.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980416
Last Updated on STN: 19980416
Entered Medline: 19980407

AB Cytokines alter neutrophil (PMN) function during inflammation, and Tumor Necrosis Factor (TNF) in vitro primes PMN such that receptor-mediated stimulation causes markedly enhanced release of arachidonic acid. We hypothesized that two **Ca(2+)-dependent** PLA2's in PMN might be activated during priming of the cell, thus affecting arachidonate release. A low molecular weight, secretory PLA2 was identified by enzymatic activity in the cell free supernates of primed or stimulated

PMN, and in PMN disrupted by nitrogen cavitation. The enzymatic activity was **calcium-dependent**, acid stable, destroyed by dithiothreitol, and blocked by anti-**sPLA2** antibodies. TNF caused secretion of **sPLA2** and also caused an increase in cell-associated **sPLA2** enzymatic activity. Activation and release were maximal with fMLP stimulation of TNF-primed PMN. Neutrophils also contained a cytosolic PLA2 (cPLA2) characterized by enzymatic activity which was **calcium dependent**, enhanced by dithiothreitol, and blocked by anti-cPLA2 antibody. TNF caused a doubling of cPLA2 enzymatic activity which was associated with phosphorylation of the enzyme as judged by a migration shift on Western blots. Thus, TNF priming of human PMN caused marked increase in fMLP stimulated AA release in parallel to enhanced activity of two different PLA2's.

L15 ANSWER 16 OF 30 MEDLINE
ACCESSION NUMBER: 97240755 MEDLINE
DOCUMENT NUMBER: 97240755 PubMed ID: 9120268
TITLE: CD16 cross-linking induces both secretory and extracellular signal-regulated kinase (ERK)-dependent cytosolic phospholipase A2 (PLA2) activity in human natural killer cells: involvement of ERK, but not PLA2, in CD16-triggered granule exocytosis.
AUTHOR: Milella M; Gismondi A; Roncaioli P; Bisogno L; Palmieri G; Frati L; Cifone M G; Santoni A
CORPORATE SOURCE: Department of Experimental Medicine and Pathology, University of Rome La Sapienza, Italy.
SOURCE: JOURNAL OF IMMUNOLOGY, (1997 Apr 1) 158 (7) 3148-54. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970506
Last Updated on STN: 19980206
Entered Medline: 19970424

AB The phospholipase A2 (PLA2) enzymes play a central role in diverse cellular processes including phospholipid digestion and metabolism, host defense, and cell signaling. We investigated the ability of CD16 clustering to trigger PLA2 and extracellular signal-regulated kinase (ERK) activation in human NK cells, as well as their possible involvement in CD16-stimulated degranulation. Both secretory (**sPLA2**) and cytosolic (cPLA2) PLA2 were rapidly activated upon CD16 cross-linking; **sPLA2** was found in the supernatant and also in a cell-associated form. cPLA2 activation was controlled by the ERK pathway as indicated by the close correlation between their kinetics of activation and by the ability of the specific MEK inhibitor, PD 098059, to abolish cPLA2 activation. CD16 stimulation also resulted in the generation of platelet-activating factor (PAF) and leukotrienes; both phospholipases contributed to their biosynthesis. Using the pharmacologic inhibitors AACOCF3, p-bromophenacyl bromide (pBPB), and PD 098059, which specifically inhibit cPLA2, **sPLA2**, and MEK, respectively, we demonstrated that the ERK signaling pathway, but not cytosolic or secretory PLA2, is required for CD16-triggered granule release.

L15 ANSWER 17 OF 30 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 97153018 MEDLINE
DOCUMENT NUMBER: 97153018 PubMed ID: 8999952
TITLE: Selective inhibition of cytosolic phospholipase A2 in activated human monocytes. Regulation of superoxide anion production and low density lipoprotein oxidation.
AUTHOR: Li Q; Cathcart M K
CORPORATE SOURCE: Department of Cell Biology, Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA.
CONTRACT NUMBER: HL51068 (NHLBI)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Jan 24) 272 (4) 2404-11. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY DATE: Entered STN: 19970306
Last Updated on STN: 19970306
Entered Medline: 19970221

AB Our previous studies have shown that monocyte activation and release of O-2 are required for monocyte-mediated low density lipoprotein (LDL) lipid oxidation. We have also found that intracellular Ca2+ levels and protein kinase C activity are requisite participants in this potentially pathogenic process. In these studies, we further investigated the mechanisms involved in the oxidation of LDL lipids by activated human monocytes, particularly the potential contributions of the cytosolic phospholipase A2 (cPLA2) signaling pathway. The most well-studied cPLA2, has a molecular mass of 85 kDa and has been reported to be regulated by both Ca2+ and phosphorylation. We found that cPLA2 protein levels and cPLA2 enzymatic activity were induced upon activation of human monocytes by opsonized zymosan. Pharmacologic inhibition of cPLA2 activity by AACOCF3, which has been reported to be a specific inhibitor of cPLA2 as compared with **sPLA2**, **caused** a dose-**dependent** inhibition of cPLA2 enzymatic activity and LDL lipid oxidation by activated human monocytes, whereas **sPLA2** activity was not affected. To corroborate these findings, we used specific antisense oligonucleotides to inhibit cPLA2. We observed that treatment with antisense oligonucleotides caused suppression of both cPLA2 protein expression and enzymatic activity as well as monocyte-mediated LDL lipid oxidation. Furthermore, antisense oligonucleotide treatment caused a substantial inhibition of O-2 production by activated human monocytes. In parallel experimental groups, cPLA2 sense oligonucleotides did not affect cPLA2 protein expression, cPLA2 enzymatic activity, O-2 production, or monoctye-mediated LDL lipid oxidation. These studies support the proposal that cPLA2 activity is required for activated monocytes to oxidize LDL lipids.

L15 ANSWER 18 OF 30 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 97292997 MEDLINE
DOCUMENT NUMBER: 97292997 PubMed ID: 9149050
TITLE: Phospholipase A2 secretion during intestinal graft ischemia.
AUTHOR: Sonnino R E; Pigatt L; Schrama A; Burchett S; Franson R
CORPORATE SOURCE: Department of Biochemistry and Molecular Biophysics, Medical College of Virginia, Virginia Commonwealth University, Richmond 23298, USA.
SOURCE: DIGESTIVE DISEASES AND SCIENCES, (1997 May) 42 (5) 972-81. Journal code: 7902782. ISSN: 0163-2116.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 19970612
Last Updated on STN: 19970612
Entered Medline: 19970604

AB The time-dependent appearance of phospholipase A2 (PLA2) activity in the preservation media of ischemic rat intestinal grafts is described. In controls, **Ca2+-dependent**, secretory PLA2 activity accumulated rapidly during the first 6 hr of ischemia, followed by a linear increase for up to 48 hr. LDH levels, by contrast, increased linearly throughout the 48 hr of ischemia. Addition of inhibitors of PLA2, cyclooxygenase, and lipooxygenase blocked accumulation of PLA2, but not LDH. PX-13, a novel PLA2 inhibitor, was most effective: 40 microM inhibited release by 86%, while 25 microM indomethacin (cyclooxygenase blocker) or nordihydroguiaretic acid (lipooxygenase blocker) inhibited 41 and 36%, respectively. That appearance of PLA2 activity, but not LDH, is attenuated by inhibitors of the eicosanoid cascade suggests a secretory event rather than leakage from dying cells. The secreted PLA2 is most likely the proinflammatory **sPLA2** that has been implicated as a stress-induced protein and priming agent in ischemia-reperfusion injury.

L15 ANSWER 19 OF 30 MEDLINE DUPLICATE 14
ACCESSION NUMBER: 97343951 MEDLINE
DOCUMENT NUMBER: 97343951 PubMed ID: 9200478

TITLE: Endotoxin induces expression of type II phospholipase A2 in macrophages during acute lung injury in guinea pigs: involvement of TNF-alpha in lipopolysaccharide-induced type II phospholipase A2 synthesis.
AUTHOR: Arbibe L; Vial D; Rosinski-Chupin I; Havet N; Huerre M; Vargaftig B B; Touqui L
CORPORATE SOURCE: Unit of Cellular Pharmacology, Associate Unit of the Pasteur Institute/INSERM 285, Paris, France.
SOURCE: JOURNAL OF IMMUNOLOGY, (1997 Jul 1) 159 (1) 391-400. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970724
Last Updated on STN: 19970724
Entered Medline: 19970714

AB Elevated levels of secretory type II phospholipase A2 (**sPLA2**-II) have been associated with a poor clinical outcome in the acute respiratory distress syndrome. This study identifies the cell source(s) and the mechanisms of **sPLA2**-II synthesis in the guinea pig model of acute respiratory distress syndrome induced by intratracheal injection of LPS. Administration of LPS led to an increase in lung membrane-associated **calcium-dependent sPLA2** activity, which was abrogated by LY311727, a selective inhibitor of **sPLA2**-II. No **sPLA2** activity was detected in the vascular compartment of the lung. LPS administration induced a parallel accumulation of **sPLA2** -II mRNA in lung tissues. In situ hybridization showed that **sPLA2** -II transcripts were synthesized in interstitial and alveolar macrophages (AM). Incubation of AM with LPS enhanced the expression of **sPLA2** -II mRNA, leading to stimulation of **sPLA2**-II synthesis and secretion. This increase was prevented by the addition of anti-TNF-alpha and anti-p55 TNF receptor Abs. Furthermore, the addition to AM of cellfree bronchoalveolar fluid collected from LPS-treated guinea pigs increased **sPLA2**-II expression, which was abrogated by anti-TNF-alpha Ab. These findings demonstrate that 1) macrophages are in vivo the major cell source of **sPLA2**-II in LPS-induced acute lung injury; 2) in contrast to that in other cell systems, regulation of LPS-induced **sPLA2**-II synthesis in AM is TNF-alpha dependent; and 3) production of TNF-alpha in the air-lung interface is an important step for **sPLA2**-II synthesis in macrophages.

L15 ANSWER 20 OF 30 MEDLINE DUPLICATE 15
ACCESSION NUMBER: 97131963 MEDLINE
DOCUMENT NUMBER: 97131963 PubMed ID: 8977420
TITLE: The rat ovarian phospholipase A2 system: gene expression, cellular localization, activity characterization, and interleukin-1 dependence.
AUTHOR: Kol S; Ruutiainen-Altman K; Ben-Shlomo I; Payne D W; Ando M; Adashi E Y
CORPORATE SOURCE: Department of Obstetrics and Gynecology, University of Maryland School of Medicine, Baltimore 21201, USA.
CONTRACT NUMBER: HD-19998 (NICHD)
HD-30288 (NICHD)
SOURCE: ENDOCRINOLOGY, (1997 Jan) 138 (1) 322-31. Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970123

AB We have previously demonstrated that interleukin-1 beta (IL-1 beta), a putative intermediary in the ovulatory process, is a potent stimulator of ovarian PG biosynthesis. In this communication, we examine the possibility that this IL-1 effect reflects in part the induction of arachidonic acid mobilization by phospholipase A2 (PLA2). Molecular probing of whole ovarian material revealed the immature rat ovary to be a site of modest

secretory PLA2 (**sPLA2**) gene expression. However, no change in ovarian **sPLA2** gene expression was noted during the periovulatory period. Comparable probing for cytosolic PLA2 (cPLA2) failed to disclose a quantifiable signal. However, in situ hybridization localized both **sPLA2** and cPLA2 (**sPLA2** > cPLA2) transcripts to the granulosa cell layer of the ovarian follicle. Treatment of cultured whole ovarian dispersates with IL-1 beta produced significant ($P < 0.01$) increments in the steady state levels of transcripts corresponding to both **sPLA2** (1.7-fold increase) and cPLA2 (5-fold increase), an effect reversed by an IL-1 receptor antagonist, suggesting mediation via a specific IL-1 receptor. Treatment with cycloheximide, a protein synthesis inhibitor, resulted in significant attenuation of the ability of IL-1 beta to up-regulate **sPLA2** and cPLA2 gene expression as well as medium PLA2 activity. Treatment with aminoguanidine, an inhibitor of inducible nitric oxide synthase, led to augmentation of the ability of IL-1 beta to up-regulate **sPLA2** and cPLA2 gene expression as well as medium PLA2 activity. Total cellular PLA2 activity proved time, cell density, and **calcium dependent**, with an optimal pH of 8.0-9.0 and K(m) values in the low micromolar range (2-5 microM). Our observations 1) establish the rat ovary as a site of **sPLA2** and cPLA2 gene expression, 2) localize the corresponding transcripts to the granulosa cell layer, and 3) establish IL-1 beta as an up-regulatory agent for ovarian **sPLA2** and cPLA2 gene expression as well as for ovarian PLA2 activity. These findings also indicate that the IL-1 effect is 1) receptor mediated, 2) contingent in part upon de novo protein biosynthesis, and 3) inhibited by nitric oxide. These observations support the proposition that PLA2 may be a key component in the IL-1-stimulated biosynthesis of ovarian PGs.

L15 ANSWER 21 OF 30 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 97343941 MEDLINE
DOCUMENT NUMBER: 97343941 PubMed ID: 9200468
TITLE: NKR-P1A stimulation of arachidonate-generating enzymes in rat NK cells is associated with granule release and cytotoxic activity.
AUTHOR: Grazia Cifone M; Roncaioli P; Cironi L; Festuccia C; Meccia A; D'Alo S; Botti D; Santoni A
CORPORATE SOURCE: Department of Experimental Medicine, University of L'Aquila, Italy.
SOURCE: JOURNAL OF IMMUNOLOGY, (1997 Jul 1) 159 (1) 309-17. Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970724
Last Updated on STN: 19970724
Entered Medline: 19970714

AB NKR-P1A protein has been implicated in the triggering of NK-mediated natural killing contributing to target cell recognition by NK cells. The aim of the present work was to assess whether NKR-P1A receptor triggering also induced arachidonic acid (AA) generation and to determine the possible role of this event on granule release and cytotoxicity. We demonstrated that activation of fresh peripheral blood rat NK cells by cross-linking with the anti-NKR-P1A 3.2.3 mAb induced **calcium-dependent** AA release, which is due to the activation of cytosolic phospholipase A2 (cPLA2), secretory phospholipase A2 (**sPLA2**), and diacylglycerol/monoacylglycerol lipase. We also documented the presence of a type II **sPLA2** activity in the supernatant fluids from NKR-P1A-activated rat NK cells, suggesting that AA and lysophospholipids could be mobilized from the outside of the cell. The involvement of AA-generating enzymes in NKR-P1A-induced cytotoxic functions was also investigated. Treatment of effector cells with arachidonyl trifluoromethylketone, a cPLA2 inhibitor; p-bromophenacylbromide, a **sPLA2** inhibitor; or RHC80267, a diacylglycerol lipase inhibitor, led to a partial inhibition of the redirected lysis against P815 target cells as well the granule content release induced by NKR-P1A cross-linking. A complete abolishment of these events was observed when the cells were simultaneously incubated with all three inhibitors. Taken together, our results support a crucial role for

the arachidonate-generating enzymes in the induction of lytic activity of NK cells directly or by leading to generation of additional mediators that can play a role in the context of NK cell activation and cytotoxic functions.

L15 ANSWER 22 OF 30 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 17
ACCESSION NUMBER: 1997:209361 CAPLUS
DOCUMENT NUMBER: 126:271648
TITLE: Phospholipase A2 inhibitors in development
AUTHOR(S): Tibes, Ulrich; Friebe, Walter-Gunar
CORPORATE SOURCE: Dep. of Preclin. Res., Boehringer Mannheim GmbH, Mannheim, D-68305, Germany
SOURCE: Expert Opinion on Investigational Drugs (1997), 6(3), 279-298
CODEN: EOIDER; ISSN: 0967-8298
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 145 refs. To date, three isoforms of phospholipase A2 (PLA2) have been identified. Of these, the two **Ca2+-dependent** isoforms, secretory (**sPLA2**) and cytosolic phospholipase A2 (cPLA2), are targets for new anti-inflammatory drugs. The catalytic mechanisms and functions of the third isoform, Ca2+-independent cytosolic phospholipase A2 (iPLA2), are unknown at present. **SPLA2** and cPLA2 are both implicated in the release of arachidonic acid and prophlogistic lipid mediators. However, recent findings provide evidence that cPLA2 is the dominant isoform in various kinds of inflammation, such as T-cell-mediated exptl. arthritis. A triple function of PLA2-derived lipid mediators has been suggested: causing immediate inflammatory signs, involvement in secondary processes, e.g., superoxide free radical (O2-) generation, apoptosis, or tumor necrosis factor-.alpha. (TNF-.alpha.)-cytotoxicity, and controlling the expression and activation of pivotal proteins implicated in inflammation and cell development, e.g., cytokines, adhesion proteins, proteinases, NF-.kappa.B, fos/jun/AP-1, c-Myc, or p21ras. In the past, research predominantly focused on the development of **sPLA2** inhibitors; however, present techniques enable discrimination of cPLA2, **sPLA2**, and iPLA2, and specific inhibitors of each of the three isoforms are likely to appear soon. Over the last decade, between 40 and 50 **sPLA2** inhibitors have been described; and the list is growing. However, of these, few have the potential for clin. success, and those that do are predominantly active site-directed inhibitors, e.g., BMS-181162, LY311727, ARL-67974, FPL67047, SB-203347, Ro-23-9358, YM-26734, and IS-741. At present, there are no likely clin. candidates emerging from the ranks of cPLA2 and iPLA2 inhibitors in development. Indications for which PLA2 inhibitors are being pursued include, sepsis, acute pancreatitis, inflammatory skin and bowel diseases, asthma, and rheumatoid arthritis. The three main obstacles to the successful development of PLA2 inhibitors include, insufficient oral bioavailability, low affinity for the enzyme corresponding to low in vivo efficacy and insufficient selectivity.

L15 ANSWER 23 OF 30 MEDLINE
ACCESSION NUMBER: 1998031571 MEDLINE
DOCUMENT NUMBER: 98031571 PubMed ID: 9366243
TITLE: Cross-talk between secretory phospholipase A2 and cytosolic phospholipase A2 in rat renal mesangial cells.
AUTHOR: Huwiler A; Staudt G; Kramer R M; Pfeilschifter J
CORPORATE SOURCE: Department of Pharmacology, Biozentrum, University of Basel, Switzerland.
SOURCE: BIOCHIMICA ET BIOPHYSICA ACTA, (1997 Oct 18) 1348 (3) 257-72.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971125
AB Incubation of rat glomerular mesangial cells with potent proinflammatory

cytokines like interleukin 1beta, (IL- 1beta) triggers the expression of a non-pancreatic secretory phospholipase A2 (**sPLA2**) and increases the formation of prostaglandin E2. We show here that **sPLA2** acts in an autocrine fashion on mesangial cells and induces a rapid activation of protein kinase C (PKC) isoenzymes delta and epsilon and of p42 mitogen-activated protein kinase (MAPK), two putative activators of cytosolic phospholipase A2 (cPLA2). **sPLA2** also activates Raf-1 kinase in mesangial cells which integrates the signals coming from PKC for further processing along the MAPK cascade. Subsequently a phosphorylation and activation of cPLA2 is observed, thus arguing for a cross-talk between the two classes of PLA2. Pretreatment of cells with either the highly specific PKC inhibitor Ro-318220 or the highly specific MAPK kinase (MEK) inhibitor PD 98059 completely blocked the **sPLA2**-induced cPLA2 activation, indicating that both kinases are essential for the cross-talk between the two types of PLA2. The effect of **sPLA2** is mimicked by lysophosphatidylcholine (LPC), a reaction product of **sPLA2** activity. LPC stimulates PKC-epsilon, Raf-1 kinase and MAPK activation as well as cPLA2 activation with a subsequent increase in arachidonic acid release from mesangial cells. These data suggest that **sPLA2** by cleaving membrane phospholipids and generating LPC and other lysophospholipids activates cPLA2 via the PKC/Raf-1/MAPK signalling pathway. Hence a network of interactions between different PLA2s is operative in mesangial cells and may contribute to the progression of glomerular inflammatory processes.

L15 ANSWER 24 OF 30 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 97424369 MEDLINE
DOCUMENT NUMBER: 97424369 PubMed ID: 9280291
TITLE: Detection of secretory phospholipase A2s related but not identical to type IIA isozyme in cultured mast cells.
AUTHOR: Murakami M; Tada K; Shimbara S; Kambe T; Sawada H; Kudo I
CORPORATE SOURCE: Department of Health Chemistry, School of Pharmaceutical Sciences, Showa University, Tokyo, Japan.
SOURCE: FEBS LETTERS, (1997 Aug 18) 413 (2) 249-54. Journal code: 0155157. ISSN: 0014-5793.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19971008
Last Updated on STN: 19971008
Entered Medline: 19970923

AB We previously reported that BALB/cJ mouse-derived bone marrow-derived mast cells (BMMC) exhibited two sequential phases of prostaglandin D2 (PGD2) generation in response to Fc(epsilon) receptor I (Fc(epsilon)RI) crosslinking and cytokine stimulation, the late phase of which was suppressed by an antibody raised against type IIA secretory phospholipase A2 (**sPLA2**). Here we report that BMMC derived from C57BL/6J mice, which are genetically deficient in type IIA **sPLA2**, display both immediate and delayed PGD2 generation normally. Lysates of C57BL/6J-derived BMMC contained a **Ca2+-dependent** PLA2 that was absorbed to a column conjugated with anti-type IIA **sPLA2** antibody and had a similar molecular mass of 14 kDa, as assessed by immunoblotting. Therefore we speculate that a **sPLA2** similar to, but distinct from, type IIA **sPLA2** would compensate for type IIA **sPLA2** deficiency in C57BL/6J-derived BMMC. We found that the two type IIA-related **sPLA2** family members, type V and type IIC sPLA2s, were expressed in BMMC as well as in rat mastocytoma RBL-2H3 cells.

L15 ANSWER 25 OF 30 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 1998047064 MEDLINE
DOCUMENT NUMBER: 98047064 PubMed ID: 9387871
TITLE: High-affinity binding sites for 125I-labelled pancreatic secretory phospholipase A2 in rat brain.
AUTHOR: Dev K K; Foged C; Andersen H; Honore T; Henley J M
CORPORATE SOURCE: Department of Anatomy, University of Bristol, Medical School, UK.
SOURCE: BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1997 Oct 3) 49 (1-2) 120-6.

Journal code: 8908640. ISSN: 0169-328X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980224
Last Updated on STN: 19980224
Entered Medline: 19980211

AB Porcine pancreatic secretory phospholipase A2 (ppsPLA2) has been shown to modulate agonist and antagonist binding to alpha-amino-3-hydroxy-5-methylisoxazolepropionate (AMPA) receptors and to effect neurotransmission in the central nervous system (CNS). To further elucidate the mechanism of action of ppsPLA2 in the CNS, the binding profile of 125I-labelled ppsPLA2 to rat whole-brain membranes was assessed. Two classes of **calcium -dependent** binding sites were detected using unlabelled ppsPLA2 as a displacer with IC50 values of 3 and 217 nM. Similar values were obtained for [125I]ppsPLA2 binding to membranes prepared from isolated cortical and hippocampal rat brain regions. [125I]ppsPLA2 binding displayed bell-shaped concentration-dependence curves to Ca2+, Zn2 + and pH. Binding was not inhibited by AMPA, the false substrate, oleoyloxyethyl phosphocholine (OOPC), or by BSA-galactose or wheat germ agglutinin. [125I]ppsPLA2 binding was reduced by treatment of the rat brain membranes with mercaptoethanol and proteinase K treatment or by their pre-incubation at 95 degrees C. These results show a different binding profile to the previously characterised snake venom **sPLA2** N-type receptors and suggest the existence of novel class of **sPLA2** N-type binding sites.

L15 ANSWER 26 OF 30 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:446230 CAPLUS
DOCUMENT NUMBER: 122:211855
TITLE: Human neutrophils store type II 14-kDa phospholipase A2 in granules and secrete active enzyme in response to soluble stimuli
AUTHOR(S): Rosenthal, M. D.; Gordon, M. N.; Buescher, E. S.; Slusser, J. H.; Harris, L. K.; Franson, R. C.
CORPORATE SOURCE: Department of Biochemistry, Eastern Virginia Medical School, Norfolk, VA, 23501-1980, USA
SOURCE: Biochemical and Biophysical Research Communications (1995), 208(2), 650-6
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Although "secretory" type II 14-kDa phospholipase A2 (**sPLA2**) activity has been described in neutrophils, direct evidence of enzyme secretion has been elusive. The authors used immunogold electron microscopy with polyclonal and monoclonal antibodies to **sPLA2** to demonstrate localization of the enzyme to granules of resting human neutrophils and translocation to phagolysosomes. Sol. stimuli such as calcium ionophore A23187 stimulate loss of cell-assocd. enzymic activity. Supernatant fluids from stimulated neutrophils lack measurable PLA2 but contain proteases which inactivate exogenous **sPLA2**. The use of .alpha.1-antitrypsin as a protease inhibitor permitted this first demonstration of secretion of PLA2 activity from stimulated human neutrophils.

L15 ANSWER 27 OF 30 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 95310925 MEDLINE
DOCUMENT NUMBER: 95310925 PubMed ID: 7540662
TITLE: Phospholipase A2 down-regulates the affinity of [3H]AMPA binding to rat cortical membranes.
AUTHOR: Dev K K; Honore T; Henley J M
CORPORATE SOURCE: Department of Anatomy, University of Bristol, Medical School, England, UK.
SOURCE: JOURNAL OF NEUROCHEMISTRY, (1995 Jul) 65 (1) 184-91.
Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199507
ENTRY DATE: Entered STN: 19950807
Last Updated on STN: 19960129
Entered Medline: 19950726

AB The effects of exogenous phospholipase A2 on the binding of alpha-[3H]amino-3-hydroxy-5-methylisoxazole-4-propionate ([3H]AMPA) to rat cortical membranes in the presence of the chaotrope potassium thiocyanate were assessed. Pretreatment of membranes with secretory phospholipase A2 (**sPLA2**) elicited a concentration-dependent decrease in specific [3H]AMPA binding due mainly to a decrease in affinity (KD). This observation, together with protease inhibitor and western blot evidence, suggest that the **sPLA2** effect is not due to proteolysis. The **sPLA2**-evoked decrease was temperature and **calcium dependent**. Inclusion of the specific inhibitor oleoyloxyethyl phosphocholine or preincubation of the enzyme with reducing agents to degrade its secondary structure significantly reduced the **sPLA2** inhibition. These results suggest that the effects of **sPLA2** arise from an enzymatic action rather than a competitive interaction at the AMPA binding site. However, arachidonic acid, a major metabolite of **sPLA2** action, did not cause a similar decrease in the affinity of [3H]AMPA binding. In contrast to the effects on [3H]AMPA binding, **sPLA2** caused an increase in [3H]CNQX binding, which is in accordance with the functionality of the AMPA receptor complex. These results suggest that **sPLA2** may play a role in the physiological and pathophysiological regulation of AMPA receptors.

L15 ANSWER 28 OF 30 MEDLINE DUPLICATE 21
ACCESSION NUMBER: 94099123 MEDLINE
DOCUMENT NUMBER: 94099123 PubMed ID: 8273580
TITLE: Secretory phospholipase A2 inhibitors and calmodulin antagonists as inhibitors of cytosolic phospholipase A2.
AUTHOR: Hope W C; Chen T; Morgan D W
CORPORATE SOURCE: Department of Bronchopulmonary Research, Hoffmann-La Roche Inc., Nutley, NJ 07110.
SOURCE: AGENTS AND ACTIONS, (1993) 39 Spec No C39-42.
Journal code: 0213341. ISSN: 0065-4299.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 19940215
Last Updated on STN: 19940215
Entered Medline: 19940131

AB Human cytosolic phospholipase A2 (cPLA2, 85 kDa) appears to be pharmacologically distinct from human secretory phospholipase A2 (**sPLA2**, 14 kDa). Marine natural products and PLA2 substrate and product analogs were potent inhibitors of human recombinant **sPLA2** (r-**sPLA2**), whereas these compounds stimulated, weakly inhibited, or had no effect on cPLA2 activity from the human monocytic cell line U937. In contrast, within a series of seven reported calmodulin (CaM) antagonists tested, significant correlations among the rank order of potencies of these compounds as inhibitors of cPLA2, r-**sPLA2**, and a **CaM-dependent** phosphodiesterase were observed. The correlated inhibitory effects of the hydrophobic CaM antagonists on cPLA2 and **sPLA2** may reflect a common feature (possibly a hydrophobic domain) shared by these two types of enzymes.

L15 ANSWER 29 OF 30 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 92335255 MEDLINE
DOCUMENT NUMBER: 92335255 PubMed ID: 1631101
TITLE: Cytosolic phospholipase A2 is coupled to hormonally regulated release of arachidonic acid.
AUTHOR: Lin L L; Lin A Y; Knopf J L
CORPORATE SOURCE: Genetics Institute, Inc., Cambridge, MA 02140.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1992 Jul 1) 89 (13) 6147-51.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208
ENTRY DATE: Entered STN: 19920904
Last Updated on STN: 20000303
Entered Medline: 19920814

AB Cytosolic phospholipase A2 (cPLA2) binds to natural membrane vesicles in a **Ca**(2+)**-dependent** fashion, resulting in the selective release of arachidonic acid, thus implicating cPLA2 in the hormonally regulated production of eicosanoids. Here we report that the treatment of Chinese hamster ovary (CHO) cells overexpressing cPLA2 with ATP or thrombin resulted in an increased release of arachidonic acid as compared with parental CHO cells, demonstrating the hormonal coupling of cPLA2. In contrast, CHO cells overexpressing a secreted form of mammalian PLA2 (**sPLA2**-II) failed to show any increased hormonal responsiveness. Interestingly, we have noted that the activation of cPLA2 with a wide variety of agents stimulates the phosphorylation of cPLA2 on serine residues. Pretreatment of cells with staurosporin blocked the ATP-mediated phosphorylation of cPLA2 and strongly inhibited the activation of the enzyme. Increased cPLA2 activity was also observed in lysates prepared from ATP-treated cells and was sensitive to phosphatase treatment. These results suggest that in addition to Ca2+, the phosphorylation of cPLA2 plays an important role in the agonist-induced activation of cPLA2.

L15 ANSWER 30 OF 30 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91230462 EMBASE
DOCUMENT NUMBER: 1991230462
TITLE: Structure of recombinant human rheumatoid arthritic synovial fluid phospholipase A2 at 2.2 .ANG. resolution.
AUTHOR: Wery J.-P.; Schevitz R.W.; Clawson D.K.; Bobbitt J.L.; Dow E.R.; Gamboa G.; Goodson Jr. T.; Hermann R.B.; Kramer R.M.; McClure D.B.; Mihelich E.D.; Putnam J.E.; Sharp J.D.; Stark D.H.; Teater C.; Warrick M.W.; Jones N.D.
CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN 46285, United States
SOURCE: Nature, (1991) 352/6330 (79-82).
ISSN: 0028-0836 CODEN: NATUAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Phospholipases A2 (PLA2s) may be grouped into distinct families of proteins that catalyse the hydrolysis of the 2-acyl bond of phospholipids and perform a variety of biological functions. The best characterized are the small (relative molecular mass .apprx. 14,000) **calcium-dependent,** secretory enzymes of diverse origin, such as pancreatic and venom PLA2s. The structures and functions of several PLA2s are known. Recently, high-resolution crystal structures of complexes of secretory PLA2s with phosphonate phospholipid analogues have provided information about the detailed stereochemistry of transition-state binding, confirming the proposed catalytic mechanism of esterolysis. By contrast, studies on mammalian nonpancreatic secretory PLA2s (s-PLA2s) have only recently begun; s-PLA2s are scarce in normal cells and tissues but large amounts are found in association with local and systemic inflammatory processes and tissue injury in animals and man. Such s-PLAs have been purified from rabbit and rat inflammatory exudate, from synovial fluid from patients with rheumatoid arthritis and from human platelets. Cloning and sequencing shows that the primary structure of the human **sPLA2** has about 37% homology with that of bovine pancreatic PLA2 and 44% homology with that of Crotalus atrox PLA2. The human s-PLA2 is an unusually basic protein, yet contains most of the highly conserved amino-acid residues and sequences characteristic of the PLA2s sequenced so far. Here we report the refined, three-dimensional crystal structure at 2.2 .ANG. resolution of recombinant human rheumatoid arthritic synovial fluid PLA2. This may aid the development of potent and specific inhibitors of this enzyme using structure-based design.

=> log y

WEST Search History

DATE: Monday, February 24, 2003

Set Name side by side	Query	Hit Count	Set Name result set
DB=USPT,PGPB,JPAB,EPAB,DWPI; THES=ASSIGNEE; PLUR=YES; OP=ADJ			
L4	L1 and phosphatidylglycerol and phosphatidylcholine	2	L4
L3	L2 and human	58	L3
L2	L1 and phospholipase	87	L2
L1	spla2	154	L1

END OF SEARCH HISTORY

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Search Results - Record(s) 1 through 2 of 2 returned.

☐ 1. Document ID: US 5552530 A

L4: Entry 1 of 2 File: USPT Sep 3, 1996

US-PAT-NO: 5552530
DOCUMENT-IDENTIFIER: US 5552530 A

TITLE: Antibodies that specifically bind to and inhibit human synovial phospholipase A.sub.2 type A

DATE-ISSUED: September 3, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Johnson; Lorin K.	Pleasanton	CA		
Seilhamer; Jeffrey J.	Milpitas	CA		
Pruzanski; Waldemar	Willowdale			CA
Vadas; Peter	Toronto			CA

US-CL-CURRENT: 530/387.9; 530/388.26, 530/389.1

ABSTRACT:

Antibodies that specifically bind to and inhibit the enzymatic activity of synovial phospholipase A.sub.2 Type A are described. The antibodies may be used in assays for detection of synovial phospholipase A.sub.2 in biological samples.

8 Claims, 18 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 18

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 5019508 A

L4: Entry 2 of 2 File: USPT May 28, 1991

US-PAT-NO: 5019508
DOCUMENT-IDENTIFIER: US 5019508 A

TITLE: Synovial phospholipases

DATE-ISSUED: May 28, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Johnson; Lorin K.	Pleasanton	CA		
Seilhamer; Jeffrey J.	Milpitas	CA		
Pruzanski; Waldemar	Ontario			CA
Vadas; Peter	Ontario			CA

US-CL-CURRENT: 435/198; 435/252.3, 435/320.1, 536/23.2, 536/23.5

ABSTRACT:

Mammalian synovial phospholipase A.sub.2 (sPLA.sub.2) enzymes are provided, as well as DNA constructs encoding these enzymes, methods of producing the enzymes recombinantly, and antibodies thereto. Therapeutic methods employing anti-synovial phospholipase antibodies are also provided, in addition to diagnositc methods and other applications of sPLA.sub.2.

25 Claims, 12 Drawing figures
Exemplary Claim Number: 12
Number of Drawing Sheets: 11

WEST

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Search Results - Record(s) 1 through 20 of 58 returned.

☐ 1. Document ID: US 20030017157 A1

L3: Entry 1 of 58 File: PGPB Jan 23, 2003

PGPUB-DOCUMENT-NUMBER: 20030017157
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030017157 A1

TITLE: Endothelial cell expression patterns

PUBLICATION-DATE: January 23, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
St. Croix, Brad	Cockeysville	MD	US	
Vogelstein, Bert	Baltimore	MD	US	
Kinzler, Kenneth W.	BelAir	MD	US	

US-CL-CURRENT: 424/155.1; 530/388.8

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 2. Document ID: US 20030008816 A1

L3: Entry 2 of 58 File: PGPB Jan 9, 2003

PGPUB-DOCUMENT-NUMBER: 20030008816
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030008816 A1

TITLE: Methods and compositions for the treatment of fibrotic conditions & impaired lung function & to enhance lymphocyte production

PUBLICATION-DATE: January 9, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Pilon, Aprile L.	Gaithersburg	MD	US	
Welch, Richard W.	Gaithersburg	MD	US	
Farrow, Jeffrey	Ellicott City	MD	US	
Melby, James	Mount Airy	MD	US	
Wiese, Laura	Germantown	MD	US	
Lohnas, Gerald	Mount Airy	MD	US	
Miele, Lucio	West Chicago	IL	US	
Antico, Gianni	Oak Park	IL	US	

US-CL-CURRENT: 514/12; 424/130.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 3. Document ID: US 20020169108 A1

L3: Entry 3 of 58 File: PGPB Nov 14, 2002

PGPUB-DOCUMENT-NUMBER: 20020169108
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020169108 A1

TITLE: Methods and compositions for the treatment of fibrotic conditions & impaired lung function & to enhance lymphocyte production

PUBLICATION-DATE: November 14, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Pilon, Aprile L.	Gaithersburg	MD	US	

US-CL-CURRENT: 514/2; 435/7.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 20020119139 A1

L3: Entry 4 of 58 File: PGPB Aug 29, 2002

PGPUB-DOCUMENT-NUMBER: 20020119139
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020119139 A1

TITLE: Cloning and recombinant expression of mammalian group XII secreted phospholipase A2

PUBLICATION-DATE: August 29, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Lazdunski, Michel	Nice		FR	
Lambeau, Gerard	Blausasc		FR	
Valentin, Emmanuel	Melun		FR	

US-CL-CURRENT: 424/94.6; 435/196, 435/320.1, 435/325, 435/69.1, 530/388.26, 536/23.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 5. Document ID: US 20020110523 A1

L3: Entry 5 of 58 File: PGPB Aug 15, 2002

PGPUB-DOCUMENT-NUMBER: 20020110523
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020110523 A1

TITLE: Methods for screening or monitoring the risk of cardiovascular disease relating to sex steroid compound or composition intake and methods for screening sex steroid compound

PUBLICATION-DATE: August 15, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Kluft, Cornelis	Sassenheim		NL	
Emeis, Josephus Jan	Boskoop		NL	

US-CL-CURRENT: 424/9.2; 435/4

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 6. Document ID: US 20020081719 A1

L3: Entry 6 of 58 File: PGPB Jun 27, 2002

PGPUB-DOCUMENT-NUMBER: 20020081719
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020081719 A1

TITLE: Inflammation inducible hybrid promoters, vectors comprising them and uses thereof

PUBLICATION-DATE: June 27, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Massaad, Charbel	Paris		FR	
Berenbaum, Francis	Gif Sur Yvette		FR	
Olivier, Jean-Luc	Paris		FR	
Salvat, Colette	Paris		FR	
Bereziat, Gilbert	Palaiseau		FR	

US-CL-CURRENT: 435/320.1; 536/23.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 7. Document ID: US 20020039757 A1

L3: Entry 7 of 58 File: PGPB Apr 4, 2002

PGPUB-DOCUMENT-NUMBER: 20020039757
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020039757 A1

TITLE: Enzyme method for detecting lysophospholipids and phospholipids and for detecting and correlating conditions associated with altered levels of lysophospholipids

PUBLICATION-DATE: April 4, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Small, Chris	Pullman	WA	US	
Parrott, Jeff	Irvine	CA	US	
Xu, Liang Zhong	Mountain View	CA	US	

US-CL-CURRENT: 435/25

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 8. Document ID: US 20020004213 A1

L3: Entry 8 of 58 File: PGPB Jan 10, 2002

PGPUB-DOCUMENT-NUMBER: 20020004213
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20020004213 A1

TITLE: Enzyme method for detecting lysophospholipids and phospholipids and for detecting and correlating conditions associated with altered levels of lysophospholipids

PUBLICATION-DATE: January 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Small, Christopher	Pullman	WA	US	
Parrott, Jeff A.	Irvine	CA	US	
Xu, Liang Zhong	Mountain View	CA	US	

US-CL-CURRENT: 435/7.91; 435/189, 435/25, 435/28

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 9. Document ID: US 20010047137 A1

L3: Entry 9 of 58 File: PGPB Nov 29, 2001

PGPUB-DOCUMENT-NUMBER: 20010047137
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010047137 A1

TITLE: Methods and apparatus for in vivo identification and characterization of vulnerable atherosclerotic plaques

PUBLICATION-DATE: November 29, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Moreno, Pedro	Lexington	KY	US	
Lodder, Robert A.	Nicholasville	KY	US	
O'Connor, William	Lexington	KY	US	
Muller, James E.	Lexington	KY	US	

US-CL-CURRENT: 600/475; 250/338.1, 250/339.01, 250/339.06, 250/339.11, 600/476, 600/477

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 10. Document ID: US 6514984 B1

L3: Entry 10 of 58 File: USPT Feb 4, 2003

US-PAT-NO: 6514984
DOCUMENT-IDENTIFIER: US 6514984 B1

TITLE: Treatment for alzheimer's disease

DATE-ISSUED: February 4, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Watanabe; August Masaru	Carmel	IN		

US-CL-CURRENT: 514/293; 514/224.5, 514/229.8, 514/250, 514/347, 514/411, 544/101, 544/250, 544/31, 544/346, 544/95, 546/87, 548/428, 548/430, 548/432, 548/441, 548/448

ABSTRACT:

A method is disclosed for the prevention and treatment of Alzheimer's disease by administering

to a human in need thereof an effective amount of a substituted tricyclic sPLA.sub.2 inhibitor.

9 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 11. Document ID: US 6472389 B1

L3: Entry 11 of 58 File: USPT Oct 29, 2002

US-PAT-NO: 6472389
DOCUMENT-IDENTIFIER: US 6472389 B1

TITLE: Pyrrolo[1,2-b] pyridazine derivatives having sPLA2 inhibitory effect

DATE-ISSUED: October 29, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ohtani; Mitsuaki	Osaka			JP
Fuji; Masahiro	Osaka			JP
Fukui; Yoshikazu	Osaka			JP
Adachi; Makoto	Osaka			JP

US-CL-CURRENT: 514/233.2; 514/248, 544/119, 544/235, 548/517, 548/527, 548/557

ABSTRACT:

The present invention provides a compound having sPLA.sub.2 inhibiting activity.

The compound represented by the formula (I): ##STR1##

wherein R.sup.1 is --(L.sup.1)--R.sup.6 wherein L.sup.1 is a divalent linking group of 1 to 18 atoms or the like, and R.sup.6 is a carbocyclic ring substituted by at least one non-interfering substituent or the like; R.sup.2 is C1 to C3 alkyl or the like; R.sup.3 is --(L.sup.2)-(acidic group); R.sup.4 and R.sup.5 are hydrogen atoms, non-interfering substituents, carbocyclic groups or the like; X is independently oxygen atom of sulfur atom; and R.sup.A is --C(.dbd.X)--C(.dbd.X)--NH.sub.2 or the like; the prodrugs thereof, their pharmaceutically acceptable salts, or their solvates, and a composition for inhibiting sPLA.sub.2 containing them as effective ingredients.

7 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 12. Document ID: US 6451839 B1

L3: Entry 12 of 58 File: USPT Sep 17, 2002

US-PAT-NO: 6451839
DOCUMENT-IDENTIFIER: US 6451839 B1

TITLE: Indole sPLA2 inhibitors

DATE-ISSUED: September 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bach; Nicholas James	Indianapolis	IN		
Dillard; Robert Delane	Zionsville	IN		
Draheim; Susan Elizabeth	Indianapolis	IN		
Mihelich; Edward David	Carmel	IN		
Suarez; Tulio	Greenwood	IN		

US-CL-CURRENT: 514/415; 514/419, 548/483, 548/507

ABSTRACT:

A class of novel indole is disclosed together with the use of such compounds for inhibiting sPLA.sub.2 mediated release of fatty acids for treatment of inflammatory diseases such as septic shock.

23 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 13. Document ID: US 6436983 B1

L3: Entry 13 of 58 File: USPT Aug 20, 2002

US-PAT-NO: 6436983
DOCUMENT-IDENTIFIER: US 6436983 B1

TITLE: Treatment for alzheimer's disease

DATE-ISSUED: August 20, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Watanabe; August M	Carmel	IN		

US-CL-CURRENT: 514/419

ABSTRACT:

This invention is a method of treating a mammal, including a human, susceptible to having Alzheimer's disease, to prevent or delay the onset of Alzheimer's disease; said method comprising administering to said mammal a prophylactically effective amount of 1H-indole-3-glycoxyamide sPLA.sub.2 inhibitor or a pharmaceutically acceptable salt, solvate or prodrug derivative thereof.

7 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 14. Document ID: US 6433001 B1

L3: Entry 14 of 58 File: USPT Aug 13, 2002

US-PAT-NO: 6433001
DOCUMENT-IDENTIFIER: US 6433001 B1

TITLE: 1H-indole-3-glyoxylamide sPLA2 inhibitors

DATE-ISSUED: August 13, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bach; Nicholas J.	Indianapolis	IN		
Dillard; Robert D.	Zionsville	IN		
Draheim; Susan E.	Indianapolis	IN		

US-CL-CURRENT: 514/419; 548/493

ABSTRACT:

A class of novel 1H-indole-3-glyoxylamides is disclosed together with the use of such indole compounds for inhibiting sPLA2 mediated release of fatty acids for treatment of conditions such as septic shock.

1 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 15. Document ID: US 6407104 B1

L3: Entry 15 of 58 File: USPT Jun 18, 2002

US-PAT-NO: 6407104
DOCUMENT-IDENTIFIER: US 6407104 B1

TITLE: Pyrrolo[1,2-a]pyrazine spla2 inhibitor

DATE-ISSUED: June 18, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ohtani; Mitsuaki	Osaka			JP
Fuji; Masahiro	Osaka			JP
Okada; Tetsuo	Osaka			JP

US-CL-CURRENT: 514/233.2; 514/248, 544/116, 544/349

ABSTRACT:

##STR1##

wherein R.sup.1 is --(L.sup.1)--R.sup.6 wherein L.sup.1 is a divalent linking group of 1 to 18 atoms or the like, and R.sup.6 is a carbocyclic ring substituted by at least one non-interfering substituent or the like; R.sup.2 is C1 to C3 alkyl, C3 to C4 cycloalkyl or the like group; R.sup.3 is --(L.sup.2)-(acidic group); R.sup.4 and R.sup.5 are hydrogen atoms, non-interfering substituents, carbocyclic groups or the like; R.sup.A is --C(.dbd.X)--C(.dbd.X)--NH.sub.2 or the like; and X is independently oxygen atom or sulfur atom; the prodrugs thereof, their pharmaceutically acceptable salts, or their solvates, and a composition for inhibiting sPLA.sub.2 containing them as effective ingredients.

24 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 16. Document ID: US 6391908 B1

L3: Entry 16 of 58 File: USPT May 21, 2002

US-PAT-NO: 6391908
DOCUMENT-IDENTIFIER: US 6391908 B1

TITLE: Oxime amide indole type sPLA2 inhibitors

DATE-ISSUED: May 21, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bach; Nicholas James	Indianapolis	IN		
Harper; Richard Waltz	Indianapolis	IN		
Kinnick; Michael Dean	Indianapolis	IN		
Lin; Ho-Shen	Indianapolis	IN		
Morin, Jr.; John Michael	Brownsburg	IN		
Richett; Michael Enrico	Indianapolis	IN		

US-CL-CURRENT: 514/419; 548/495

ABSTRACT:

A class of novel oxime indoles is disclosed together with the use of such compounds for inhibiting sPLA.sub.2 mediated release of fatty acids for treatment of inflammatory diseases such as septic shock.

19 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 17. Document ID: US 6384041 B1

L3: Entry 17 of 58 File: USPT May 7, 2002

US-PAT-NO: 6384041
DOCUMENT-IDENTIFIER: US 6384041 B1

TITLE: Bicyclic sPLA2 inhibitors

DATE-ISSUED: May 7, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Hutchison; Darrell Robert	Indianapolis	IN		
Martinelli; Michael John	Zionsville	IN		
Wilson; Thomas Michael	Speedway	IN		

US-CL-CURRENT: 514/265.1; 544/280

ABSTRACT:

The compounds are of the class of pyrrolo[2,3-d]pyrimidines useful for inhibiting sPLA.sub.2 mediated release of fatty acids for treatment of diseases such as septic shock.

13 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 18. Document ID: US 6353128 B1

L3: Entry 18 of 58 File: USPT Mar 5, 2002

US-PAT-NO: 6353128
DOCUMENT-IDENTIFIER: US 6353128 B1

TITLE: Phenyl acetamides as sPLA2 inhibitors

DATE-ISSUED: March 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Goodson, Jr.; Theodore	Indianapolis	IN		
Harper; Richard Waltz	Indianapolis	IN		
Herron; David Kent	Indianapolis	IN		

US-CL-CURRENT: 560/41; 558/173, 558/49, 560/39, 562/41, 562/51

ABSTRACT:

A class of novel phenyl acetamides is disclosed together with the use of such compounds for inhibiting sPLA.sub.2 mediated release of fatty acids for treatment of conditions such as septic shock.

12 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 19. Document ID: US 6340699 B1

L3: Entry 19 of 58 File: USPT Jan 22, 2002

US-PAT-NO: 6340699
DOCUMENT-IDENTIFIER: US 6340699 B1

TITLE: SPLA2 inhibitor compounds for treatment of disease

DATE-ISSUED: January 22, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Macias; William Louis	Indianapolis	IN		

US-CL-CURRENT: 514/419

ABSTRACT:

The present invention is directed to compounds for treating inflammatory bowel disease. More specifically, the present invention is directed to 1H-indole-3-glyoxyamide compounds a sPLA.sub.2 inhibitors for treating inflammatory bowel disease.

12 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 20. Document ID: US 6274616 B1

US-PAT-NO: 6274616
DOCUMENT-IDENTIFIER: US 6274616 B1

TITLE: N,N-diethylglycolamido ester prodrugs of indole sPLA2 inhibitors

DATE-ISSUED: August 14, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Denney; Michael L	Franklin	IN		
Morin, Jr.; John M	Brownsburg	IN		
Sall; Daniel J	Greenwood	IN		
Sawyer; Jason S	Indianapolis	IN		

US-CL-CURRENT: 514/419

ABSTRACT:

The compound, ((3-(2-amino-1,2-dioxoethyl)-1-((1,1'-biphenyl-3-ylmethyl)-2-methyl-1H-indol-4-yl)oxy)acetic acid N,N-diethylglycolamido ester, is disclosed together with its use as a highly bioavailable indole compound for inhibiting sPLA.sub.2 mediated release of fatty acids for treatment of conditions such as septic shock.

6 Claims, 0 Drawing figures
Exemplary Claim Number: 1

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☐ 21. Document ID: US 6274578 B1

L3: Entry 21 of 58 File: USPT Aug 14, 2001

US-PAT-NO: 6274578
DOCUMENT-IDENTIFIER: US 6274578 B1

TITLE: sPLA2 inhibitor ester

DATE-ISSUED: August 14, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Denney; Michael Lyle	Franklin	IN		
Morin; John Michael	Brownsburg	IN		
Sall; Daniel Jon	Indianapolis	IN		
Sawyer; Jason Scott	Indianapolis	IN		

US-CL-CURRENT: 514/235.2; 544/144

ABSTRACT:

The compound, ((3(2-amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl)oxy)ac etic acid N-morpholino ester, is disclosed together with its use as a highly bioavailable indole sPLA.sub.2 inhibitor compound.

2 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 22. Document ID: US 6255063 B1

L3: Entry 22 of 58 File: USPT Jul 3, 2001

US-PAT-NO: 6255063
DOCUMENT-IDENTIFIER: US 6255063 B1

TITLE: Disease conditions by measuring lysophosphatidic acid

DATE-ISSUED: July 3, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Small; Christopher L.	Pullman	WA		
Parrott; Jeff A.	Irvine	CA		
Xu; Liang Shong	Mountain View	CA		

US-CL-CURRENT: 435/18; 435/21, 435/25, 435/26, 436/71

ABSTRACT:

The present invention is an enzymatic method and diagnostic kits for detecting and quantifying the presence of one or more lysophospholids in a sample of bodily fluid taken from a test subject. The method uses enzymes in a two step assay and may be used to detect disease conditions associated with altered levels of lysophospholipids and to correlate such conditions with altered levels of lysophospholipids.

5 Claims, 10 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 23. Document ID: US 6252084 B1

L3: Entry 23 of 58 File: USPT Jun 26, 2001

US-PAT-NO: 6252084
DOCUMENT-IDENTIFIER: US 6252084 B1

TITLE: 1H-indole-3-acetamide sPLA2 inhibitors

DATE-ISSUED: June 26, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bach; Nicholas J.	Indianapolis	IN		
Dillard; Robert D.	Zionsville	IN		
Draheim; Susan E.	Indianapolis	IN		
Hermann; Robert B.	Indianapolis	IN		
Schevitz; Richard W.	Indianapolis	IN		

US-CL-CURRENT: 548/113; 548/127, 548/252, 548/253, 548/254, 548/483, 548/494, 548/495, 548/496

ABSTRACT:

A class of novel 1H-indole-3-acetamides is disclosed together with the use of such indole compounds for inhibiting sPLA.sub.2 mediated release of fatty acids for treatment of conditions such as septic shock.

2 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 24. Document ID: US 6248553 B1

L3: Entry 24 of 58 File: USPT Jun 19, 2001

US-PAT-NO: 6248553
DOCUMENT-IDENTIFIER: US 6248553 B1

TITLE: Enzyme method for detecting lysophospholipids and phospholipids and for detecting and correlating conditions associated with altered levels of lysophospholipids

DATE-ISSUED: June 19, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Small; Christopher L.	Pullman	WA		
Parrott; Jeff A.	Pullman	WA		
Xu; Liang Zhong	Pullman	WA		

US-CL-CURRENT: 435/25; 435/15, 435/26, 436/71

ABSTRACT:

The present invention is an enzymatic method and diagnostic kits for detecting and quantifying the presence of one or more lysophospholids in a sample of bodily fluid taken from a test subject. The method uses enzymes in a two step assay and may be used to detect disease conditions associated with altered levels of lysophospholipids and to correlate such conditions with altered levels of lysophospholipids.

20 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 25. Document ID: US 6214876 B1

L3: Entry 25 of 58 File: USPT Apr 10, 2001

US-PAT-NO: 6214876
DOCUMENT-IDENTIFIER: US 6214876 B1

TITLE: Indene-1-acetamide sPLA2 inhibitors

DATE-ISSUED: April 10, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Dillard; Robert D.	Zionsville	IN		
Hagishita; Sanji	Gose			JP
Ohtani; Mitsuaki	Nara			JP

US-CL-CURRENT: 514/563; 514/561, 562/428, 562/441

ABSTRACT:

Indene-1-acetamide compounds of the general formula (I) below; ##STR1##

inhibit sPLA.sub.2 mediated release of fatty acids and are useful for treatment of conditions such as septic shock.

12 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw. Desc | Image

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☐ 26. Document ID: US 6177426 B1

L3: Entry 26 of 58 File: USPT Jan 23, 2001

US-PAT-NO: 6177426
DOCUMENT-IDENTIFIER: US 6177426 B1

TITLE: Morpholino-N-ethyl ester prodrugs of indole sPLA2 inhibitors

DATE-ISSUED: January 23, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Denney; Michael L	Franklin	IN		
Morin; John M	Brownsburg	IN		
Sall; Daniel J	Greenwood	IN		
Sawyer; Jason S	Indianapolis	IN		

US-CL-CURRENT: 514/235.2; 544/144

ABSTRACT:

The compound, ((3(2-amino-1,2-dioxoethyl)-1-((1,1'-biphenyl)-3-ylmethyl)-2-methyl-1H-indol-4-yl)oxy)acetic acid morpholino-ethyl ester, is disclosed together with its use as a highly bioavailable indole compound for inhibiting sPLA.sub.2 mediated release of fatty acids for treatment of conditions such as septic shock.

5 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 27. Document ID: US 6175021 B1

L3: Entry 27 of 58 File: USPT Jan 16, 2001

US-PAT-NO: 6175021
DOCUMENT-IDENTIFIER: US 6175021 B1

TITLE: 1H-indole-3-glyoxylamide sPLA2 inhibitors

DATE-ISSUED: January 16, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bach; Nicholas J.	Indianapolis	IN		
Dillard; Robert D.	Zionsville	IN		
Draheim; Susan E.	Indianapolis	IN		

US-CL-CURRENT: 548/493; 548/495

ABSTRACT:

A class of novel 1H-indole-3-glyoxylamides is disclosed together with the use of such indole compounds for inhibiting sPLA.sub.2 mediated release of fatty acids for treatment of conditions such as septic shock.

2 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 28. Document ID: US 6166062 A

L3: Entry 28 of 58 File: USPT Dec 26, 2000

US-PAT-NO: 6166062
DOCUMENT-IDENTIFIER: US 6166062 A

TITLE: Pharmaceutical compositions containing phospholipase inhibitor

DATE-ISSUED: December 26, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Confer; William Lester	Indianapolis	IN		
Tai; Hideaki	Osaka			JP

US-CL-CURRENT: 514/419; 514/415

ABSTRACT:

A lyophilized pharmaceutical composition is described which contains Sodium [[3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-phenylmethyl)-1H-indol-4-yl]oxy]ace tate, a Solubilizer, and a Stabilizer. Such compositions are storage stable and readily dissolve in aqueous medium to give injectable solution for treatment of sepsis, etc.

24 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments

KWIC | Draw Desc | Image

☐ 29. Document ID: US 6140327 A

L3: Entry 29 of 58 File: USPT Oct 31, 2000

US-PAT-NO: 6140327
DOCUMENT-IDENTIFIER: US 6140327 A

TITLE: Morpholino-n-ethyl ester derivative of an indole sPLA.sub.2 inhibitor

DATE-ISSUED: October 31, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Sawyer; Jason Scott	Indianapolis	IN		
Morin, Jr.; John Michael	Brownsburg	IN		
Beight; Douglas Wade	Frankfort	IN		
Sall; Daniel Jon	Greenwood	IN		
Buben; John Andrew	Indianapolis	IN		

US-CL-CURRENT: 514/235.2; 544/144

ABSTRACT:

The compound, ((3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl)oxy)ac etic acid morpholino-N-ethyl ester, is disclosed together with its use as a highly bioavailable indole compound for inhibiting sPLA.sub.2 mediated release of fatty acids for treatment of conditions such as septic shock.

5 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments

KWIC | Draw Desc | Image

☐ 30. Document ID: US 5972972 A

L3: Entry 30 of 58 File: USPT Oct 26, 1999

US-PAT-NO: 5972972
DOCUMENT-IDENTIFIER: US 5972972 A

TITLE: Pyrazoles as human non-pancreatic secretory phospholipase A.sub.2 inhibitors

DATE-ISSUED: October 26, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mihelich; Edward D.	Carmel	IN		
Suarez; Tulio	Greenwood	IN		
Hite; Gary A.	Indianapolis	IN		
Doman; Peter J.	Bossiney			GB
Willetts; Stuart E.	Bossiney			GB

US-CL-CURRENT: 514/341; 514/255.05, 514/307, 514/404, 544/405, 546/144, 546/276.1, 548/368.7

ABSTRACT:

A class of novel pyrazoles is disclosed together with the use of such compounds for inhibiting sPLA.sub.2 mediated release of fatty acids for treatment of conditions such as septic shock.

10 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

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☐ 31. Document ID: US 5916922 A

L3: Entry 31 of 58 File: USPT Jun 29, 1999

US-PAT-NO: 5916922
DOCUMENT-IDENTIFIER: US 5916922 A

TITLE: Phenyl glyoxamides as SPLA2 inhibitors

DATE-ISSUED: June 29, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Goodson, Jr.; Theodore	Indianapolis	IN		
Harper; Richard Waltz	Indianapolis	IN		
Herron; David Kent	Indianapolis	IN		

US-CL-CURRENT: 514/563; 514/114, 514/119, 514/506, 514/517, 514/538, 514/539, 514/541, 514/561, 514/562, 514/567, 514/576, 514/618, 514/621, 514/622, 558/169, 558/170, 558/174, 558/49, 558/50, 558/60, 560/36, 560/37, 560/42, 560/9, 562/15, 562/42, 562/426, 562/441, 562/442, 562/451, 562/455, 562/456, 564/162, 564/169, 564/171

ABSTRACT:

A class of novel phenyl glyoxamides is disclosed together with the use of such compounds for inhibiting sPLA.sub.2 mediated release of fatty acids for treatment of conditions such as septic shock.

13 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 32. Document ID: US 5622828 A

L3: Entry 32 of 58 File: USPT Apr 22, 1997

US-PAT-NO: 5622828
DOCUMENT-IDENTIFIER: US 5622828 A

TITLE: High-affinity oligonucleotide ligands to secretory phospholipase A2 (sPLA.sub.2)

DATE-ISSUED: April 22, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Parma; David H.	Boulder	CO		
Gold; Larry	Boulder	CO		

US-CL-CURRENT: 435/6; 435/91.2, 536/22.1

ABSTRACT:

This invention discloses high-affinity oligonucleotide ligands to human secretory phospholipase A2 (sPLA.sub.2), specifically RNA ligands having the ability to bind to sPLA.sub.2, and the methods for obtaining such ligands.

11 Claims, 0 Drawing figures
Exemplary Claim Number: 1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 33. Document ID: US 5552530 A

L3: Entry 33 of 58 File: USPT Sep 3, 1996

US-PAT-NO: 5552530
DOCUMENT-IDENTIFIER: US 5552530 A

TITLE: Antibodies that specifically bind to and inhibit human synovial phospholipase A.sub.2 type A

DATE-ISSUED: September 3, 1996

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Johnson; Lorin K.	Pleasanton	CA		
Seilhamer; Jeffrey J.	Milpitas	CA		
Pruzanski; Waldemar	Willowdale			CA
Vadas; Peter	Toronto			CA

US-CL-CURRENT: 530/387.9; 530/388.26, 530/389.1

ABSTRACT:

Antibodies that specifically bind to and inhibit the enzymatic activity of synovial phospholipase A.sub.2 Type A are described. The antibodies may be used in assays for detection of synovial phospholipase A.sub.2 in biological samples.

8 Claims, 18 Drawing figures
Exemplary Claim Number: 1
Number of Drawing Sheets: 18

34. Document ID: US 5019508 A

L3: Entry 34 of 58 File: USPT May 28, 1991

US-PAT-NO: 5019508
DOCUMENT-IDENTIFIER: US 5019508 A

TITLE: Synovial phospholipases

DATE-ISSUED: May 28, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Johnson; Lorin K.	Pleasanton	CA		
Seilhamer; Jeffrey J.	Milpitas	CA		
Pruzanski; Waldemar	Ontario			CA
Vadas; Peter	Ontario			CA

US-CL-CURRENT: 435/198; 435/252.3, 435/320.1, 536/23.2, 536/23.5

ABSTRACT:

Mammalian synovial phospholipase A.sub.2 (sPLA.sub.2) enzymes are provided, as well as DNA constructs encoding these enzymes, methods of producing the enzymes recombinantly, and antibodies thereto. Therapeutic methods employing anti-synovial phospholipase antibodies are also provided, in addition to diagnositc methods and other applications of sPLA.sub.2.

25 Claims, 12 Drawing figures
Exemplary Claim Number: 12
Number of Drawing Sheets: 11

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

35. Document ID: EP 846687 A1

L3: Entry 35 of 58 File: EPAB Jun 10, 1998

PUB-NO: EP000846687A1
DOCUMENT-IDENTIFIER: EP 846687 A1
TITLE: Pyrazoles as human non-pancreatic secretory phospholipase A2 inhibitors

PUBN-DATE: June 10, 1998

INVENTOR-INFORMATION:

NAME	COUNTRY
DOMAN, PETER JEREMY	GB
HITE, GARY ALAN	US
MIHELICH, EDWARD DAVID	US
SUAREZ, TULIO	US
WILLETTS, STUART EDMUND	GB

INT-CL (IPC): C07 D 231/44; C07 D 401/04; C07 D 401/14; C07 D 403/04; C07 D 417/14; C07 D 409/14; C07 D 409/12; A61 K 31/415; A61 K 31/44; A61 K 31/47; A61 K 31/50
EUR-CL (EPC): C07D231/44

ABSTRACT:

CHG DATE=19990617 STATUS=O> A class of novel pyrazoles is disclosed together with the use of

such compounds for inhibiting sPLA2 mediated release of fatty acids for treatment of conditions such as septic shock.

☐ 36. Document ID: WO 9627604 A1

L3: Entry 36 of 58 File: EPAB Sep 12, 1996

PUB-NO: WO009627604A1
DOCUMENT-IDENTIFIER: WO 9627604 A1
TITLE: HIGH-AFFINITY OLIGONUCLEOTIDE LIGANDS TO SECRETORY PHOSPHOLIPASE A2(SPLA2)

PUBN-DATE: September 12, 1996

INVENTOR-INFORMATION:

NAME	COUNTRY
GOLD, LARRY	US
PARMA, DAVID	US
JANJIC, NEBOJSA	US
LOCHRIE, MICHAEL	US

INT-CL (IPC): C07 H 21/02; C07 H 21/04; C12 P 19/34; C12 Q 1/68
EUR-CL (EPC): G01N033/569; C12Q001/68, C07K014/47

ABSTRACT:

CHG DATE=19990617 STATUS=O>Methods are described for the identification and preparation of high-affinity nucleic acid ligands to human secretory phospholipase A2(sPLA2) and human immunodeficiency virus type-1 GAG (HIV-1 GAG). Included in the invention are specific RNA ligands to sPLA2 and HIV-1 GAG identified by the SELEX method. Also included are high-affinity modified RNA ligands and ssDNA ligands to vascular endothelial growth factor (VEGF).

☐ 37. Document ID: WO 200279154 A1

L3: Entry 37 of 58 File: DWPI Oct 10, 2002

DERWENT-ACC-NO: 2003-019019
DERWENT-WEEK: 200301

TITLE: New substituted carbazole derivative useful in the treatment of e.g. asthma

INVENTOR: HARPER, R W; LIN, H ; RICHETT, M E

PRIORITY-DATA: 2001US-279300P (March 28, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200279154 A1	October 10, 2002	E	092	C07D209/88

INT-CL (IPC): A61 K 31/403; A61 P 29/00; C07 D 209/88; C07 D 401/04; C07 D 405/04; C07 D 409/04

ABSTRACTED-PUB-NO: WO 200279154A
BASIC-ABSTRACT:

NOVELTY - Substituted carbazole derivatives (I) are new.

DETAILED DESCRIPTION - Substituted carbazole derivatives of formula (I), their solvates and salts are new.

ring Z = cyclohexenyl or phenyl;

R20 = R80 or A'';

R80 = -1-20C alkyl, -2-20C alkenyl, -2-20C alkynyl, carbocyclic radical or heterocyclic radical (all optionally substituted by at least one non-interfering substituents);

A'' = -(L)-R80;

L = divalent linking group of 1-12 atoms selected from C, H, N, O and S;

R21 = non-interfering substituent;

f, j = 1-3;

R1 = -NHNR30R31, -NR30R31 or -CONR30R31;

R30, R31 = H or -1-6C alkyl;

R2' = -CONR40R41;

R40 = -OH, -O-1-8C alkyl, -O-2-8C alkenyl, -O-3-8C cycloalkyl, -O-aryl or -O-1-8C alkylaryl;

R41 = H, -1-8C alkyl, -2-8C alkenyl, -3-8C cycloalkyl, aryl or -1-8C alkylaryl; and

R3' = carbocyclic, heterocyclic radicals (optionally substituted by non-interfering substituents) or a non-interfering substituent;

provided that he combination of atoms in -(L)- are selected from the group consisting of:

(i) C and H;

(ii) S;

(iii) O;

(iv) 1-2 N and H;

(v) C, H and 1 S; and

(vi) C, H and O.

INDEPENDENT CLAIMS are also included for:

(1) use of (I) in the manufacture of a medicament for alleviating the pathological effects of secretory phospholipase A2 (sPLA2) related diseases; and

(2) preparation of (I).

ACTIVITY - Antibacterial; Immunosuppressive; Antiinflammatory; Tranquilizer; Vulnerary; Antiasthmatic; Antirheumatic; Antiarthritic; Osteopathic; Cerebroprotective; Antiallergic; Antigout; Uropathic; Ophthalmological; Antisickling; Tuberculostatic; Analgesic; Antilipemic; Dermatological.

MECHANISM OF ACTION - Secretory Phospholipase A2 (sPLA2) Inhibitor.

In a chromogenic assay for evaluating inhibition of recombinant human secreted phospholipase A2 (using the method described by L. J. Reynolds, L. L. Hughes, and E. A. Dennis, Analytical Biochemistry, 204, pp. 190-197, 1992.), ((5-carbamoyl-9-(phenylmethyl)carbazol-4-yl)oxy)-N-(phe- nyloxy)acetamide (Ia) inhibited sPLA2 with an IC50 of 12 nM.

USE - In the manufacture of a medicament for the treatment of sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, asthma, rheumatoid arthritis, osteoarthritis, acute bronchitis, chronic bronchitis, inflammatory bowel disease, apoptosis, stroke, cystic fibrosis, allergic rhinitis, acute bronchiolitis, chronic bronchiolitis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonoccocal

arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with vasculitic syndromes, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's disease, systemic lupus erythrematosis or relapsing polychondritis and related diseases in a mammal (particularly human) (all claimed).

ADVANTAGE - (I) Are potent inhibitors of human sPLA2 mediated release of fatty acids and thereby inhibit or prevent the arachidonic acid cascade and its deleterious products.

☐ 38. Document ID: AU 200233928 A WO 200250030 A2

L3: Entry 38 of 58 File: DWPI Jul 1, 2002

DERWENT-ACC-NO: 2002-627284
DERWENT-WEEK: 200269

TITLE: New cycloalkyl fused indole compounds useful as secretory phospholipase A2 inhibitors are used to treat inflammatory diseases such as septic shock

INVENTOR: BEIGHT, D W; KINNICK, M D ; LIN, H ; MORIN, J M J ; RICHETT, M E ; SALL, D J ; SAWYER, J S ; SMITH, E C R

PRIORITY-DATA: 2000US-256397P (December 18, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 200233928 A	July 1, 2002		000	C07D209/00
WO 200250030 A2	June 27, 2002	E	174	C07D209/00

INT-CL (IPC): C07 D 209/00

ABSTRACTED-PUB-NO: WO 200250030A
BASIC-ABSTRACT:

NOVELTY - Cycloalkyl fused indole compounds (I) or their salts, solvates or prodrugs are new.

DETAILED DESCRIPTION - Cycloalkyl fused indole compounds of formula (I) or their salts, solvates or prodrugs are new.

n = 1 - 3;

R1 = T or -(L)-R80;

R80, T = 2-20C (halo)alkyl, 2-20C alkenyl, 2-20C alkynyl, carbocyclic radical or heterocyclic radical (all optionally substituted by at least one non-interfering substituent);

L = divalent linking group of 1-12 atoms comprising either (a) C and H only, (b) S only, (c) O only, (d) N and H only, (e) C, H and S only, or (f) C, H or O only;

R2 = H or a group containing 1-10 non-hydrogen or hydrogen atoms;

R3 = -(L3)-Z;

L3 = bond, -CH2-, -O-, -S-, -NH- or -C(=O)-;

Z = -C(=NORa)-C(=X)(NH2), -C(=X)-CONH2 or -C(Ra)2-;

X = O or S;

Ra = H, 1-8C alkyl, aryl, 1-8C alkaryl, 1-8C alkoxy, aralkyl or -CN;

R4 = H, CONH2, CONHR4b, -(La)-(acidic group of formula -COOH, -5-tetrazolyl, -SO3H, -C(=O)-NH-S(=O)2-R81, OH-C(=O)-(substituted phenyl), -C(=O)-OH, COOH, -COONa, -COOK or formula (i) - (v)), -(Lh)-(N-hydroxyfunctional amide group) or -(Lc)-(acylamino acid (of formula -C(O)-N(R4c)(R4d)) group);

La = acid linker of length 1-8;

Lh = N-hydroxyfunctional amide linker (of formula -C(O)-N(R4a)(R4b)) of length 1-8;

Lc = -(Q2-C(R40)2)-;

Q2 = -(CH2)-, -O-, -NH-, -C(O)- or -S-;

R40 = H, 1-8C alkyl, 1-8C alkaryl, 1-8C alkoxy, aralkyl or halo;

R4a = OH, 1-6C alkoxy or aryloxy;

R4b = H or 1-8C alkyl, aryl, 7-14C aralkyl, 7-14C alkaryl, 3-8C cycloalkyl, 1-8C alkoxyalkyl (all optionally substituted by halo, -CF3, -OH, 1-8C alkyl, amino, carbonyl or -CN);

R4c = H, 1-6C alkyl, 1-6C alkoxy, (hetero)aryl, -CF3;

NR4d = amino acid residue of natural or unnatural amino acid with N being part of the amino group of the amino acid;

R5 = H, non-interfering substituent;

R6 = non-interfering substituent;

R'80 = metal or 1-8C alkyl;

R81 = organic substituent or -CF3.

INDEPENDENT CLAIMS are also included for:

(1) A method for treatment of a human afflicted with inflammatory disease involving administering (I) or its salts, solvates or prodrugs.

(2) A method of inhibiting secretory phospholipase A2 (sPLA2) mediated release of fatty acid by contacting sPLA2 with (I);

(3) Use of a pharmaceutical composition comprising (I) or its mixtures for the manufacture of a medicament for the treatment of inflammatory diseases; and

(4) A method for the manufacture of a medicament for the treatment or prevention of inflammatory diseases involving administering (I) or its salt, solvates or prodrug.

ACTIVITY - Antiinflammatory; Antibacterial; Immunosuppressive; Respiratory-Gen; Tranquilizer; Vulnerary; Antiasthmatic; Antiallergic; Antirheumatic; Antiarthritic; Cerebroprotective; Osteopathic; Antigout; Uropathic; Ophthalmological; Antipsoriatic; Tuberculostatic; Virucide; Antifungal; Analgesic; Antipyretic; and Dermatological.

MECHANISM OF ACTION - Secretory phospholipase A2 (sPLA2) mediated release of fatty acid inhibitor.

A reaction mixture (0.2 ml) containing 1 mM diheptanoyl thio-PC substrate, 0.29 mm Triton X-100 (non-ionic detergent aqueous solution) and 0.12 mM 5,5'-dithiobis-2-nitrobenzoic acid (DTNB) at pH 7.5 was added to all the wells of 96 well microtiter plates. 2-((3-(2-amino-1,2-dioxoethyl)-2-methyl-1-benzyl-1,6,7,8-tetrahydrocyclopent(g)indol-4-yl)oxy)acetic acid (A) (10 micro l) was added to the wells and mixed for 20 seconds. sPLA2 (50 nanograms) was added and the plates were incubated at 40 deg. C for 30 minutes. The IC50 value of (A) was determined by diluting (A) to a final concentration of 45 - 0.35 ug/ml. The IC50 of (A) was 0.010 micro M.

USE - (I) is used for the treatment of humans afflicted with inflammatory disease, for inhibiting secretory phospholipase A2 (sPLA2) mediated release of fatty acid and for alleviating the pathological effects of inflammatory diseases. The composition containing (I) is used in the manufacture of a medicament for the treatment of inflammatory diseases (all claimed). The inflammatory diseases are inflammatory bowel disease, sepsis, septic shock, adult respiratory distress syndrome, trauma, pancreatitis, trauma-induced shock, asthma, bronchial

asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute and chronic bronchitis, acute and chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enteropathic spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, reactive arthropathy, infectious or post-infectious arthritis, gonoccocal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with vasculitic syndromes, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, psuedo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (e.g. charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's disease, systemic lupus erythrematosis and relapsing polychondritis and related diseases.

ADVANTAGE - The compounds have potent and selective effectiveness as inhibitors of mammalian secretory phospholipase A2 (sPLA2).

☐ 39. Document ID: WO 200250028 A2 AU 200237655 A

L3: Entry 39 of 58 File: DWPI Jun 27, 2002

DERWENT-ACC-NO: 2002-528443
DERWENT-WEEK: 200270

TITLE: New benz(f)indole compounds useful as secretory phospholipase A2 inhibitors are used to treat inflammatory diseases e.g. septic shock

INVENTOR: BEIGHT, D W; KINNICK, M D ; LIN, H ; MORIN, J M J ; RICHETT, M E ; SALL, D J ; SAWYER, J S ; SMITH, E C R

PRIORITY-DATA: 2000US-256281P (December 18, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200250028 A2	June 27, 2002	E	097	C07D209/00
AU 200237655 A	July 1, 2002		000	C07D209/00

INT-CL (IPC): A61 K 31/40; A61 P 29/00; C07 D 209/00

ABSTRACTED-PUB-NO: WO 200250028A
BASIC-ABSTRACT:

NOVELTY - Benz(f)indole compounds (I), or its salts, solvates or prodrugs are new.

DETAILED DESCRIPTION - Benz(f)indole compounds of formula (I), or its salts, solvates or prodrugs are new.

R1 = T or -(L)-R80;

R80, T = 2-20C halo(alkyl), 2-20C alkenyl, 2-20C alkynyl, carbocyclic radical or heterocyclic radical (all optionally substituted by at least one non-interfering substituent);

L = divalent linking group of 1-12 atoms comprising either (a) C and H only, (b) S only, (c) O only, (d) N and H only, (e) C, H and S only, or (f) C, H or O only;

R2 = H or a group containing 1-10 non-hydrogen or hydrogen atoms;

R3 = -(L3)-Z;

L3 = bond, -CH2-, -O-, -S-, -NH- or -C=O-;

Z = -C(=NORa)-C(=X)(NH2), -C(=X)-C(=O)NH2 or -C(Ra)2-C(=X)(NH2);

X = O or S;

Ra = H, 1-8C alkyl, aryl, 1-8C alkaryl, 1-8C alkoxy, aralkyl or -CN;

R4 = H, CONH2, CONHR4b, -(La)-(acidic group of formula -COOH-5-tetrazolyl, -SO3H, -C(=O)-NH-S(=O)2-R81, OH-C(=O)-(substituted phenyl), -C(=O)-OH, COOH, -COONa, -COOK or formula (i) - (v)), -(Lh)-(N-hydroxyfunctional amide group) or -(Lc)-(acylamino acid (of formula -C(O)-N(R4c)(R4d)) group);

La = acid linker of length 1-8;

Lh = N-hydroxyfunctional amide linker of length 1-8 (where the N-hydroxyfunctional amide is -C(O)-N(R4a)(R4b));

Lc = -(Q-C(R40)2)-;

Q2 = -(CH2)-, -O-, -NH-, -C(O)- or -S-;

R40 = H, 1-8C alkyl, 1-8C alkaryl, 1-8C alkoxy, aralkyl or halo;

R4a = OH, 1-6C alkoxy or aryloxy;

R4b = H or 1-8C alkyl, aryl, 7-14C aralkyl, 7-14C alkaryl, 3-8C cycloalkyl, 1-8C alkoxyalkyl (all optionally substituted by halo, -CF3, -OH, 1-8C alkyl, amino, carbonyl or -CN);

R4c = H, 1-6C alkyl, 1-6C alkoxy, (hetero)aryl, -CF3;

NR4d = amino acid residue of natural or unnatural amino acid with N being part of the amino group of the amino acid;

R5 = H, non-interfering substituent;

R6 - R9 = non-interfering substituent;

R'80 = metal or 1-8C alkyl;

R81 = organic substituent or -CF3.

INDEPENDENT CLAIMS are also included for:

(1) a method for treatment of a human afflicted with inflammatory disease involving administering (I) or its salt, solvate or prodrug derivatives (preferably 2-((3-(2-amino-1,2-dioxoethyl)-1-benzyl-2-ethyl-1H-benz(f)ind- ol-4-yl)oxy)acetic acid ethyl ester, 2-((3-(2-amino-1,2-dioxoethyl)-1-benz- yl-2-ethyl-1H-benz(f)indol-4-yl)oxy)acetic acid benzyl ester or 2-((3-(2-amino-1,2-dioxoethyl)-1-benzyl-2-ethyl-1H-benz(f)indol-4-yl)oxy)-acetic acid);

(2) a method of inhibiting secretory phospholipase A2 (sPLA2) mediated release of fatty acid by contacting sPLA2 with (I);

(3) a method of treating mammals including humans to alleviate the pathological effects of inflammatory diseases;

(4) use of a pharmaceutical composition comprising (I) or its mixtures for the manufacture of a medicament for the treatment of inflammatory diseases; and

(5) a method for the manufacture of a medicament for the treatment or prevention of inflammatory diseases involving administering (I) or its salt, solvates or prodrug.

ACTIVITY - Antiinflammatory; antibacterial; immunosuppressive; respiratory-gen; tranquilizer; vulnerary; antiasthmatic; antiallergic; antirheumatic; antiarthritic; cerebroprotective; osteopathic; antigout; uropathic; ophthalmological; antipsoriatic; tuberculostatic; virucide; antifungal; analgesic; antipyretic; and dermatological.

MECHANISM OF ACTION - Secretory phospholipase A2 (sPLA2) mediated release of fatty acid inhibitor.

A reaction mixture (0.2 ml) containing 1 mM diheptanoyl thio-PC substrate, 0.29 mm Triton X-100 (non-ionic detergent aqueous solution) and 0.12 mM 5,5'-dithiobis-2-nitrobenzoic acid (DTNB) at pH 7.5 was added to all the wells of 96 well microtiter plates. 2-((3-(2-amino-1,2-dioxoethyl)-1-benz- yl-2-ethyl-1H-benz(f)indol-4-yl)oxy)acetic acid (A) (10 micro l) was added to the wells and mixed for 20 seconds. sPLA2 (50 nanograms) was added and

the plates were incubated at 40 deg. C for 30 minutes. The IC50 value of (A) was determined by diluting (A) to a final concentration of 45 - 0.35 micro g/ml. The IC50 of (A) was 1.06 micro M.

USE - In pharmaceutical composition for the treatment of humans afflicted with inflammatory disease, for inhibiting secretory phospholipase A2 (sPLA2) mediated release of fatty acid and for alleviating the pathological effects of inflammatory diseases. The composition containing (I) is used in the manufacture of a medicament for the treatment of inflammatory diseases (all claimed). The inflammatory diseases are inflammatory bowel disease, sepsis, septic shock, adult respiratory distress syndrome, trauma, pancreatitis, trauma-induced shock, asthma, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute and chronic bronchitis, acute and chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enteropathic spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, reactive arthropathy, infectious or post-infectious arthritis, gonoccocal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with vasculitic syndromes, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, psuedo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (e.g. charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's disease, systemic lupus erythrematosis and relapsing polychondritis and related diseases.

ADVANTAGE - The compounds have potent and selective effectiveness as inhibitors of mammalian secretory phospholipase A2 (sPLA2).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Clip Img | Image

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☐ 40. Document ID: WO 200212249 A2 AU 200180461 A

L3: Entry 40 of 58 File: DWPI Feb 14, 2002

DERWENT-ACC-NO: 2002-280687
DERWENT-WEEK: 200244

TITLE: New pyrrole compounds are human pancreatic secretory phospholipase A2 inhibitors used for treating inflammatory diseases e.g. septic shock, stroke and arthritis

INVENTOR: BEIGHT, D W; MORIN, J M J ; SAWYER, J S ; SMITH, E C R

PRIORITY-DATA: 2000US-223398P (August 4, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200212249 A2	February 14, 2002	E	078	C07D495/04
AU 200180461 A	February 18, 2002		000	C07D495/04

INT-CL (IPC): A61 K 31/407; A61 P 29/00; C07 D 209/00; C07 D 333/00; C07 D 495/04; C07 D 495/04; C07 D 333:00; C07 D 209:00

ABSTRACTED-PUB-NO: WO 200212249A
BASIC-ABSTRACT:

NOVELTY - Pyrrole compounds (I) are new.

DETAILED DESCRIPTION - Pyrrole compounds of formula (I) and their salts, solvates and prodrugs are new.

A = S, SO, SO2, O or NR;

R = non-interfering substituent;

R1 = 7-20C alkyl, 7-20C haloalkyl, 7-20C alkenyl, 7-20C alkynyl, carbocyclyl or heterocyclyl (all optionally substituted) or -(L1)-R11;

L1 = divalent linking group of 1-8 atoms;

R11 = 7-20C alkyl, 7-20C haloalkyl, 7-20C alkenyl, 7-20C alkynyl, carbocyclyl or heterocyclyl (all optionally substituted);

R2 = H or a group containing 1-4 non-hydrogen atoms and any required hydrogen atoms;

R3 = -(L3)-Z;

L3 = a bond, -CH2-, -O-, -S-, -NH-, or -C(=O)-;

Z = -C(=NORa)-C(=X)-NH2, -C(=X)-C(=O)-NH2 or -C(Ra)(Ra)-C(=X)-NH2;

X = O or S;

Ra = H, 1-8C alkyl, aryl, 1-8C alkaryl, 1-8C alkoxy, aralkyl or -CN;

R4 = H, WR4e, -(La)-(acidic group), -(Lh)-(N-hydroxyfunctional amide group) or -(Lc)-(acylamino acid group);

W = O, S or NH;

R4e = alkyl, aryl or alkylaryl;

La = an acid linker having an acid linker length of 1-8;

Lh = N-hydroxyfunctional amide linker having an N-hydroxyfunctional amide linker having the linker length of 1-8;

Lc = acylamino acid linker having a linker length of 1-8, and

R5 = H, non-interfering substituent or -(La)-(acidic group).

ACTIVITY - Antiinflammatory; Antibacterial; Tranquilizer; Vulnerary; Antipsoriatic; Antipyretic; Tuberculostatic; Immunosuppressive; Vasotropic; Antiasthmatic; Antiallergic; Antiarthritic; Antirheumatic; Cerebroprotective; Osteopathic; Antigout; Uropathic; Ophthalmological; Virucide; Fungicide; Analgesic; Antilipemic; Dermatological.

MECHANISM OF ACTION - Human non-pancreatic secretory phospholipase A2 inhibitor.

Inhibition (IC50) of human secreted PLA2 by 2-(6-benzyl-5-ethyl-6H-thieno(-2,3-b)pyrrol-4-yl)-2-oxoacetamide was determined as given in assay of Laure J. Reynolds, Lori L. Hughes, and Edward A Dennis, Analytical Biochemistry, 204, pp. 190-197 (1992) and was 5.5 mu M.

USE - Used for the treatment of inflammatory diseases (claimed) e.g. inflammatory bowel disease, sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, trauma induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathies, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathic spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonococcal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with vasculitic syndromes, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathies, pseudo gout, nonarticular rheumatism, bursitis, tenosynomitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathies, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behcet's Disease, systemic Iupus erythematosis, and relapsing polychondritis.

ADVANTAGE - (I) Exhibit potent and selective effectiveness as inhibitors of mammalian sPLA2 and inhibit sPLA2 mediated release of fatty acid, thus inhibiting or preventing the arachidonic acid cascade and its deleterious products.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Clip Img | Image

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Terms	Documents
L2 and human	58

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Search Results - Record(s) 41 through 58 of 58 returned.

☐ 41. Document ID: WO 200208189 A1 AU 200172234 A

L3: Entry 41 of 58 File: DWPI Jan 31, 2002

DERWENT-ACC-NO: 2002-195863
DERWENT-WEEK: 200236

TITLE: New amino acid derivatives useful for the treatment of inflammatory disease or condition e.g. rheumatic arthritis

INVENTOR: CLARK, C I; FAIRLIE, D P ; HANSFORD, K ; MCGEARY, R P ; REID, R C ; STOERMER, M J

PRIORITY-DATA: 2000AU-0001669 (November 24, 2000), 2000AU-0008965 (July 24, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200208189 A1	January 31, 2002	E	109	C07D209/22
AU 200172234 A	February 5, 2002		000	C07D209/22

INT-CL (IPC): A61 K 31/198; A61 K 31/405; A61 K 31/41; A61 K 31/4172; A61 K 31/4406; A61 K 31/662; A61 P 29/00; C07 C 235/12; C07 C 237/16; C07 D 209/22; C07 D 213/56; C07 D 233/26; C07 D 257/04; C07 F 9/40

ABSTRACTED-PUB-NO: WO 200208189A
BASIC-ABSTRACT:

NOVELTY - Amino acid derivatives are new.

DETAILED DESCRIPTION - Amino acid derivative of formula (I), its salt, derivative or prodrug is new.

X = CRR'CO2H, CRR'-tetrazolyl, CRR'SO3H, CRR'P(O)(OH)2, CRR'P(O)(OH)(OR''), CHRCH2CO2H, CHRCH2-tetrazolyl, CHRCH2SO3H, CHRCH2P(O)(OH)2, CHRCH2P(O)(OH)(OR''), OP(O)(OH)R', NRSO3H, NRP(O)(OH)2, NRP(O)(OH)(OR'');

R'' = alkyl, alkenyl, alkynyl, acyl, arylalkyl, cycloalkylalkyl, heterocyclylalkyl(all optionally substituted);

R and R' = H or R'';

Q = -C(O)Z, -C(O)-NHZ, -C(O)-NH-OZ, -S(O)2Z, -S(O)-Z, -P(O)(OH)Z or -P(O)(OH)OZ;

Y and Z = (CH2)m-aa-(CH2)n-B, -(CH2)m-aa-(CH2)n-A-(CH2)o-B, -(CH2)p-A-(CH2)q-A'-(CH2)r-B or -(CH2)s-B;

m = 0 or 1;

n-r = 0 - 15;

s = 5 - 15;

aa = amino acid side chain residue;

A and A' = O, S, NH, NRa, NHC(O), NRaC(O), CH2, CHRa, CHNH2, C(O), C(O)O, C(O)NH, OC(O) or CH=CH;

Ra = alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, arylalkyl, cycloalkylalkyl or heterocyclylalkyl (all optionally substituted);

B = alkyl, alkenyl, alkynyl, aryl, heterocyclyl, cycloalkyl, aryloxy, heterocyclyloxy, cycloalkoxy (all optionally substituted), H, halo, CO2H.

INDEPENDENT CLAIMS are also included for the following:

(1) preparation of (I) from D-amino acid involving:

(a) derivatizing the amino acid chain to form the group Y;

(b) extending the C-terminus of the amino acid to form the group X; and

(c) derivatizing the amino terminus of the amino acid to form the group Q. The steps a) - c) may be carried out in any order; and

(2) use of (I) in the manufacture of a medicament for the treatment or prophylaxis of an inflammatory disease or condition.

ACTIVITY - Antirheumatic; antiarthritic; neuroprotective; osteopathic; antipsoriatic; antiinflammatory; dermatological; antiulcer; immunosuppressive; antiarteriosclerotic; cytostatic; hypotensive; antiasthmatic; antiallergic; vasotropic; cardiant; nootropic; gynecological; analgesic; antidiabetic; protozoacide; antibacterial; ophthalmological.

MECHANISM OF ACTION - Secretory phospholipase A2 (SPLA2) inhibitor. (RS)-6-phenyl-4-(8-phenyl-octanoylamino)-hexanoic acid was evaluated for inhibition of human non-pancreatic sPLA2 as described in Reynolds, L.J., Hughes, L.L., Dennis, E.A., Anal Biochem., 204, 190(1992). and the IC50 value at a concentration of 1 - 10 (preferably 1) micro M was found to be 1.5 micro M.

USE - For the treatment or prophylaxis of an inflammatory disease or condition e.g. rheumatoid arthritis, multiple sclerosis, osteoarthritis, psoriasis, surgical adhesions, Crohn's disease, dermatitis, ulcers, lupus, immune complex disease, cystic fibrosis, atherosclerosis, fibrosis, bowel disease, hypotension, asthma, allergy, reperfusion injury, myocardial infarct, ischemic disease, Alzheimer's disease, dysmenorrhoea, diabetes (type I), pancreatitis, pulmonary conditions, malaria, dermatitis, adult respiratory distress syndrome (ARDS), sepsis, uveitis, lung injuries, vascular diseases, synovitis, peritonitis, cancer, allergies, chronic lung diseases, myocardial infarct, meningitis, retinitis and transplantation and graft rejection (claimed); for inhibiting the activity of phospholipase in an animal or mammal.

ADVANTAGE - (I) regulates not just phospholipid digestion, but also both transcellular and intracellular communications involved in diverse physiological functions as well as in disease development. (I) has a IC50 value for human non-pancreatic sPLA2 inhibition at a concentration of at most 50 mu m.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Clip Img | Image
KWIC | Draw Desc

☐ 42. Document ID: WO 200205796 A2 AU 200172915 A

L3: Entry 42 of 58 File: DWPI Jan 24, 2002

DERWENT-ACC-NO: 2002-241494
DERWENT-WEEK: 200236

TITLE: Preventing sepsis comprises initiating administration to a patient susceptible to sepsis, an sPLA2 inhibitor compound prior to occurrence of injury causing conditions

INVENTOR: LOH, A; MACIAS, W L ; SKERJANEC, S

PRIORITY-DATA: 2000US-256398P (December 18, 2000), 2000US-218928P (July 14, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200205796 A2	January 24, 2002	E	152	A61K031/00
AU 200172915 A	January 30, 2002		000	A61K031/00

INT-CL (IPC): A61 K 31/00; A61 K 31/403; A61 K 31/404; A61 K 31/5377; A61 K 45/06; A61 P 31/02

ABSTRACTED-PUB-NO: WO 200205796A
BASIC-ABSTRACT:

NOVELTY - Use of secretory phospholipase A2 (sPLA2) inhibitor compounds (I) for treating and/or preventing sepsis involving administration of (I) within a specific time interval, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(A) preventing sepsis in a mammal including a human, comprises initiating administration to a patient susceptible to sepsis, an sPLA2 inhibitor compound (I) prior to occurrence of injury causing conditions;

(B) methods of preventing or treating sepsis;

(C) use of (I) for the manufacture of a medicament for treating sepsis; and

(D) use of compounds of formula (I') or (I'') or their salts, solvates and prodrugs, in the manufacture of a medicament for treating or preventing sepsis in a patient afflicted with sepsis or susceptible to sepsis;

X = O;

R1 = 7-20C alkyl or a group of formula (a)-(c); ;

R10 = halo, 1-10C alkyl, 1-10C alkoxy, -S-(1-10C alkyl) or halo(1-10C)alkyl;

t = 0-5;

R2 = H, halo, cyclopropyl, methyl, ethyl or propyl;

R4, R5 = H, a non-interfering substituent and the group, -(La)-(acidic group);

at least one of R4 and R5 = (La)-(acidic group);

(acidic group) = CO2H, SO3H, or P(O)(OH)2;

-(La)- = an acid linker with the proviso that;

-(La)- for R4 = selected from OCH2, SCH2, NHCH2, CH2CH2, OC(Me) or a group of formula (d); ;

R103 = a non-interfering substituent;

(La) for R5 = selected from OC(R84)(R85)(CH2)n, SC(R84)(R85)(CH2)n, NHC(R84)(R85)(CH2)n or CH2C(R84)(R85)(CH2)n;

R84, R85 = H, 1-10C alkyl, aryl, 1-10C alkaryl, 1-10C arylalkyl, carboxy, carbalkoxy or halo;

R6, R7 = H or non-interfering substituents;

non-interfering substituents = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 7-12C arylenalkyl, 7-12C alkaryl, 3-8C cycloalkyl, 3-8C cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, 1-6C alkoxy, 2-6C alkenyloxy, 2-6C alkynyloxy, 2-12C alkoxyalkyl, 2-12C alkoxyalkyloxy, 2-12C alkylcarbonyl, 2-12C alkylcarbonylamino, 2-12C alkoxyamino, 2-12C alkoxyaminocarbonyl, 2-12C alkylamino, 1-6C alkylthio, 2-12C alkylthiocarbonyl, 1-6C alkylsulfinyl, 1-6C alkylsulfonyl, 2-6C haloalkoxy, 1-6C haloalkylsulfonyl, 2-6C haloalkyl, 1-6C hydroxyalkyl, C(O)O(1-6C alkyl), (CH2)nO(1-6C alkyl), benzyloxy, phenoxy, phenylthio, (CONHSO2R), CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, (CH2)nCO2H, Cl, CN, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, OH, hydroxyamino, iodo, nitro, phosphono, SO3H, thioacetal, thiocarbonyl or 1-6C carbonyl;

n = 1-8;

Y1 = O, NH, NR1 or S;

R10 = halo, 1-10C alkyl, 1-10C alkoxy, S-1-10C alkyl or halo-1-10C alkyl;

t = 0-5;

R31-R34, R31'-R34' = H, CONR101R102, alkyl, alkylaryl, aryl, alkylheteroaryl, haloalkyl, alkylCONR101R102, a non-interfering substituent or (La')-(acidic group 2);

La' = OCH2, SCH2, NCH2, CH2CH2, OMe, group (d), OC(R84)(R85)(CH2)n', SC(R84)(R85)(CH2)n', NHC(R84)(85)(CH2)n' or CH2C(R84)(R85)(CH2)n';

n' = 1 or 2;

acidic group 2 = COOH, SO3H, CO2NR101R102 or P(O)(OH)2;

R101, R102 = H, alkyl, aryl, heteroaryl or haloalkyl; and

R = H or alkyl;

provided that at least one of R31-R34 is the acid group (La')-(acidic group 2).

N.B. R103 is defined but does not appear in the formulae or list of definitions.

ACTIVITY - Antibacterial; immunosuppressive.

MECHANISM OF ACTION - sPLA2 inhibitor.

USE - For treating and/or prevention of sepsis or septic shock.

☐ 43. Document ID: WO 200205808 A1 AU 200172210 A

L3: Entry 43 of 58 File: DWPI Jan 24, 2002

DERWENT-ACC-NO: 2002-188505
DERWENT-WEEK: 200236

TITLE: Composition useful in treating mense-related symptoms such as uterine contraction and pain comprises a phospholipase inhibitor

INVENTOR: FAIRLIE, D P; SHIELS, I A ; TAYLOR, S M

PRIORITY-DATA: 2000AU-0008764 (July 14, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200205808 A1	January 24, 2002	E	055	A61K031/195
AU 200172210 A	January 30, 2002		000	A61K031/195

INT-CL (IPC): A61 K 31/195; A61 K 31/675; A61 P 15/00; A61 P 15/06

ABSTRACTED-PUB-NO: WO 200205808A
BASIC-ABSTRACT:

NOVELTY - A composition comprises a phospholipase inhibitor (A) and a carrier.

ACTIVITY - Gynecological; Analgesic; Antimigraine.

MECHANISM OF ACTION - Uterine contractions modulator; Eicosanoid synthesis blocker; phospholipase A2 inhibitor; non-pancreatic sPLA2 inhibitor.

The rat uterus when removed from rat and placed in an organ bath the uterus contracts rhythmically. The force of contraction varies with the profile of sex hormones produced by animal at different stages of the sexual cycle. An inhibitor (S)-5-(4-benzyl-phenylsulfanyl)-4-(7-phenylhep- tanoylamino)-pentanoic acid (I) was tested for its ability to inhibit spontaneous and oxytocin induced contractions of female rat uterus. (I) showed greatest activity when examined with uteri treated with oestrogen plus progesterone (average 53% inhibition at 1 nM).

Maximum inhibition of contraction by all drugs was seen in (I) averaging 75% inhibition at 10 nM.

USE - For treating, alleviating or reducing mense-related symptoms such as uterine contraction, pain, blood loss, dysmenorrhea, menstrual migraine, menorrhagia, premature uterine expulsion of a foetus or embryo, impending abortion or miscarriage (claimed).

ADVANTAGE - The composition is effective in treatment of menstrual side effects. The phospholipases A2 are 100 times more effective in inhibiting uterine contractions compared to non-steroidal anti-inflammatory drugs (NSAIDS). The tocolytic composition is efficacious for suppression of uterine contractions in human and also for management of birth in animals such as cattle.

44. Document ID: WO 200200641 A2 AU 200168051 A

L3: Entry 44 of 58 File: DWPI Jan 3, 2002

DERWENT-ACC-NO: 2002-130867
DERWENT-WEEK: 200235

TITLE: New benzo(b)thiophene compounds are secretory phospholipase A2 inhibitors, for treating inflammatory disorders e.g. arthritis, inflammatory bowel disease, adult respiratory distress syndrome and asthma

INVENTOR: KINNICK, M D; LIN, H ; MARTINELLI, M J ; MORIN, J M ; RICHETT, M E

PRIORITY-DATA: 2000US-214566P (June 28, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200200641 A2	January 3, 2002	E	132	C07D333/00
AU 200168051 A	January 8, 2002		000	C07D333/00

INT-CL (IPC): C07 D 333/00

ABSTRACTED-PUB-NO: WO 200200641A
BASIC-ABSTRACT:

NOVELTY - Benzo(b)thiophene compounds (I) are new.

DETAILED DESCRIPTION - Benzo(b)thiophene compounds of formula (I) and their salts, solvates and prodrugs are new.

R2 = H or a group containing 1-4 non-H atoms plus any required H atoms;

R3 = -(L3)-Z;

L3 = -CH2-, -O-, -S-, -NH- or -C(O)-; and

Z = -C(O)C(O)NHRa, -C(=NORa)C(=X)NH2, -C(=X)NHRa or -C(Ra)(Ra')C(=X)NH2;

X = O or S;

Ra, Ra' = H, 1-8C alkyl, aryl, 1-8C alkaryl, 1-8C alkoxy, aralkyl or CN;

R4 = H or -(Lx)-Y;

Lx = linker of length 1-8 (sic);

Y = acidic group, N-hydroxyfunctional amide group or acylamino group;

R5 = H, a non-interfering substituent, or (La)-acidic group;

La = acidic linker of length 1-8 (sic); and

R6, R7 = H, non-interfering substituent, or carbocyclic or heterocyclic radical (both optionally substituted by non-interfering groups).

ACTIVITY - Antiinflammatory; Antibacterial; Immunosuppressive; Gastrointestinal ; Respiratory; Vulnerary; Antiasthmatic; Antiallergic; Antiarthritic; Antirheumatic; Vasotropic; Cerebroprotective; Osteopathic, Antigout; Antipsoriatic; Dermatological; Tuberculostatic; Virucide; Fungicide; Antisickling; Hemostatic; Antilipemic; Antithyroid; Antipyretic.

MECHANISM OF ACTION - Secretory phospholipase A2 (sPLA2) inhibitor.

In a chromogenic assay procedure (see L. J. Reynolds et. al., Anal. Biochem., 204, 190-197, 1992) to determine inhibition of human sPLA2, 2-((3-(aminooxoacetyl)-2-ethylbenzo(b)thiopen-4-yl)oxy)-acetic acid (Ib) displayed an IC50 value of 1.41 micro M.

USE - (I) Are useful in inhibiting sPLA2 mediated release of fatty acids in the treatment and alleviation of symptoms of inflammatory diseases (all claimed) e.g. inflammatory bowel disease, sepsis, septic shock, adult respiratory distress syndrome (ARDS), pancreatitis, trauma-induced shock, asthma, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathis, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enteropathic spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, reactive arthropathy, infectious or postinfectious arthritis, gonoccocal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with vasculitic syndromes, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathis, pseudo gout, nonarticular rheumatism, bursitis, tenosynomitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathies, hyperlipoproteinemia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behcet's Disease, systemic lupus erythematosus, or relapsing polychondritis and related diseases.

☐ 45. Document ID: WO 200190195 A1 AU 200114187 A

L3: Entry 45 of 58 File: DWPI Nov 29, 2001

DERWENT-ACC-NO: 2002-097648
DERWENT-WEEK: 200243

TITLE: Antibodies recognizing parts of X-type phospholipase A2 and their use in immunoassays for diagnosis of cancer and Alzheimer's disease

INVENTOR: HANASAKI, K; IMAGAWA, K ; MASUTA, K

PRIORITY-DATA: 2000JP-0152967 (May 24, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200190195 A1	November 29, 2001	J	052	C07K016/40
AU 200114187 A	December 3, 2001		000	C07K016/40

INT-CL (IPC): A61 K 39/395; A61 P 43/00; C07 K 16/40; G01 N 33/53; G01 N 33/573; G01 N 33/574

ABSTRACTED-PUB-NO: WO 200190195A
BASIC-ABSTRACT:

NOVELTY - Antibodies recognizing parts of secretory X-type phospholipase A2, are new.

DETAILED DESCRIPTION - Antibodies are new which recognize:

(a) the N-terminal propeptide sequence (-11 Glu to -1 Arg) (I); or

(b) the active peptide sequence (1 Gly to 123 Asp) (II) of human secretory X-type phospholipase A2 (sPLA2).

INDEPENDENT CLAIMS are also included for the following:

(1) cover polypeptides containing sequences (I) or (II), and their use as reference antigens;

(2) a method for the assay of (I) or (II) using the antibodies;

(3) a method for the diagnosis of sPLA2-associated diseases using the assay method;

(4) kits for the assay method; and

(5) drug compositions for the treatment of sPLA2-associated diseases which contain antibodies to (II).

ACTIVITY - Cytostatic; nootropic; neuroprotective; hepatotropic.

MECHANISM OF ACTION - Antibody inhibition.

USE - The antibodies are used for the diagnosis and treatment of sPLA2-associated diseases including cancer of the colon, lung, liver, stomach, kidney, gall bladder, prostate and pancreas, Alzheimer's disease and liver cirrhosis.

ADVANTAGE - The antibodies bind either to the N-terminal propeptide sequence or the active sequence of sPLA2 allowing determination of the relative amounts of proenzyme and active enzyme present. The antibodies bound to the active enzyme will also suppress the activity of the enzyme.

DESCRIPTION OF DRAWING(S) - The graph shows a plot of relative absorption at 450 nm against propeptide concentration for Enzyme Linked Immunosorbant Assay assay of human X-type PLA2 propeptide using polyclonal rabbit anti-human X-type sPLA2 antibody (immobilized) and goat anti-rabbit IgG antibody (peroxidase-labelled). Drawing contains non-English language text.

☐ 46. Document ID: EP 1156050 A2

L3: Entry 46 of 58 File: DWPI Nov 21, 2001

DERWENT-ACC-NO: 2002-149399
DERWENT-WEEK: 200220

TITLE: New substituted tricyclic compounds useful for the treatment of e.g. septic shock

INVENTOR: BACH, N J; BASTIAN, J A ; BEIGHT, D W ; KINNICK, M D ; MARTINELLI, M J ; MIHELICH, E D ; MORLIN, J M ; SALL, D J ; SAWYER, J S ; SMITH, E C R ; SUAREZ, T ; WANG, Q ; WILSON, T M

PRIORITY-DATA: 1998US-0062165 (April 17, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1156050 A2	November 21, 2001	E	070	C07D513/04

INT-CL (IPC): A61 K 31/40; C07 D 471/04; C07 D 491/04; C07 D 513/04

ABSTRACTED-PUB-NO: EP 1156050A
BASIC-ABSTRACT:

NOVELTY - Substituted tricyclic compounds are new.

DETAILED DESCRIPTION - Substituted tricyclic compounds of formula (I), its racemate, solvate, tautomer, optical isomer, prodrug derivative or salt is new.

A = phenyl or pyridyl (where N is at 5-, 6-, 7- or 8- position);

B and D = N or C;

Z = cyclohexenyl, phenyl, pyridyl (where N is at 1-, 2- or 3-position) or a 6-membered heterocyclic ring having one heteroatom S or O at the 1-, 2- or 3-position and N at the 1-, 2-, 3- or 4-position;

a = single or double bond;

R20 = T, T' or (L)-R80;

T = 5-20C (-alkyl, -alkenyl or -alkynyl), carboxylic radical or heterocyclic radical;

T' = T substituted with at least one non-interfering substituent;

L = a divalent linking group of 1-12 atoms selected from O, H, C, N or S(where the combination of atoms in L is (i) C or H; (ii) only S; (iii) only O; (iv) 1-2 N, and H; (v) C, H and S; and (vi) C, H and O);

R80 = T or T';

R21 = a non-interfering substituent;

R1 = -NHNH2, -NH2 or CONH2;

R2 = -OH or -O(CH2)tR5;

R5 = H, CN, -NH2, -CONH2, -CONR9R10-NHSO2R15, -CONHSO2R15, phenyl optionally substituted with Q or -(La)-acidic group;

R15 = 1-6C alkyl or CF3;

Q = -CO2H or -CO2-1-4C alkyl;

-(La) = an acid linker having an acid linker length of 1-7;

t = 1 - 5;

R3 = non-interfering substituent, carboxylic radical optionally substituted with non-interfering substituent or heterocyclic radical optionally substituted with non-interfering substituent.

one of B or D is N and the other is C; provided that one of A or Z is heterocyclic ring; when D = N, then Z is a group containing S or O at 1-, 2- or 3-position and N at 1-, 2-, 3- or 4-position.

ACTIVITY - Antibacterial; immunosuppressive; antirheumatic; antiarthritic; osteopathic; cerebroprotective; antiasthmatic; antiinflammatory; tranquilizer; vulnerary; antiallergic; antigout; uropathic; opthalmological; antipsoriatic; antisickling; antilipemic.

MECHANISM OF ACTION - Secretery phospholipase A2(SPLA2) mediated release of fatty acids inhibitor; arachidonic acid cascade and its deleterious product inhibitor. (R,S)-(9-benzyl-4-carbamoyl-3-thia-1,2,3,4-tetrahydroc- arbazol-5-yl)oxyacetic acid was tested as inhibitors of recombinant human secreted phospholipase A2 in the chromogenic assay as described in . Analysis of Human Synovial Fluid Phospholipase A2 on short chain phosphatidylcholine-mixed micelles: Development of a spectrophotometric Assay suitable for a Microtiterplate Reader, by Laure J. Reynolds, Lori L. Hughes and Edward A. Dennis, Analytical biochemistry, 204, pp. 190 - 197, 1992 and was found to be effective at concentration of less than 100 micro M.

USE - For the manufacture of a medicament for alleviating or inhibiting the pathological effects of SPLA2 related diseases; inhibiting SPLA2 mediated release of fatty acid and preventing the arachidonic acid cascade and its deleterious products; and for treating inflammatory bowel disease, apoptosis, sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonoccocal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with vasculitic syndromes, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, systemic lupus erythrematosis, or relapsing polychondritis; and related diseases.(all claimed)

47. Document ID: EP 1265607 A2 WO 200166110 A2 AU 200129252 A

L3: Entry 47 of 58 File: DWPI Dec 18, 2002

DERWENT-ACC-NO: 2002-017311
DERWENT-WEEK: 200301

TITLE: Treating an animal afflicted with renal dysfunction, e.g. acute or chronic renal failure, comprises administering secretory phospholipase A2 inhibitors

INVENTOR: MACIAS, W L; MEADOR, V P

PRIORITY-DATA: 2000US-188039P (March 9, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1265607 A2	December 18, 2002	E	000	A61K031/40
WO 200166110 A2	September 13, 2001	E	160	A61K031/40
AU 200129252 A	September 17, 2001		000	A61K031/40

INT-CL (IPC): A61 K 31/40

ABSTRACTED-PUB-NO: WO 200166110A
BASIC-ABSTRACT:

NOVELTY - Treating an animal afflicted with renal dysfunction comprises administering secretory phospholipase A2 (sPLA2) inhibitors.

DETAILED DESCRIPTION - (A) Treatment of an animal afflicted with renal dysfunction comprises administering a composition including compounds selected from: 1H-indole-3-glyoxylamide, 1H-indole-3-hydrazide, 1H-indole-3-acetamide, 1H-indole-1-glyoxylamide, 1H-indole-1-hydrazide, 1H-indole-1-acetamide, indolizine-1-acetamide, indolizine-1-acetic acid hydrazide, indolizine-1-glyoxylamide, indene-1-acetamide, indene-1-acetic acid hydrazide, indene-1-glyoxylamide, carbazole, tetrahydrocarbazole, pyrazole, phenyl glyoxamide, pyrrole, naphthyl glyoxamide, naphthyl acetamide, phenyl acetamide, 9H-carbazole and/or 9-benzylcarbazole.

INDEPENDENT CLAIMS are also included for the following:

(B) methods of treating an animal afflicted with renal dysfunction;

(C) a pharmaceutical composition comprising an sPLA2 inhibitor useful for the treatment of renal dysfunction;

(D) use of an sPLA2 inhibitor in combination with therapeutic agents and or procedures selected from dialysis treatment to remove harmful toxins; drugs to restore salt and water balance; for the delay, prevention and/or treatment of acute or chronic renal failure;

(E) use of an sPLA2 inhibitor in combination with atrial naturetic factor (ANF) for the delay, prevention and/or treatment of acute and chronic renal failure in a mammal;

(F) use of an sPLA2 in combination with erythropoetin to stimulate red cell production in a mammal;

(G) use of an sPLA2 inhibitor in combination with OKT3 (RTM) to prevent kidney rejection or reduce the symptoms associated with administration of OKT3 (RTM);

(H) use of an sPLA2 inhibitor selected from the compounds in (A) except 9H-carbazole and/or 9-benzylcarbazole, for the manufacture of a medicament for treating renal dysfunction;

(I) use of compounds of formula (Va)-(Ve) for the manufacture of a medicament for treating renal dysfunction;

R = H, alkyl, aryl or heteroaryl;

(J) use of a composition including compounds selected from:
1-(9H-benzylcarbazol-1-halo-4-yloxy-5-alkylamido)alkylacetate,
1-(9H-benzylcarbazol-4-yloxy-5-alkylamido)alkylacetate,
1-(9H-benzylcarbazol-1-halo-4-yloxy-5-alkylamido)acetic acid and/or
1-(9H-benzylcarbazol-4-yloxy-5-alkylamido)acetic acid for the manufacture of a medicament for the therapeutic treatment of renal dysfunction.

ACTIVITY - Nephrotropic; antibacterial; antiinflammatory; immunosuppressive.

MECHANISM OF ACTION - sPLA2 inhibitor.

USE - For treating renal dysfunction including acute or chronic renal failure, and disease states that lead to renal failure e.g. acute nephritis, nephrotic syndrome, pyuria, auria, oliguria, uremia, bilateral arterial occlusion, acute tubular necrosis, acute uric acid nephropathy, hypovolemia, acute bilateral upper tract obstruction, hypocalcemic nephropathy, hemolytic uremic syndrome, acute urinary retention, scleroderma, hypersensitivity nephropathy, malignant nephrosclerosis, essential and mixed cryoimmunoglobulinemia, and azotemia. For the delay or prevention of acute renal failure (by combining sPLA2 inhibitors with ANF atrial naturetic factor). For reducing the symptoms associated with administration of OKT3 (RTM) (a monoclonal antibody for preventing graft rejection by T3 antigens produced by human T cells). sPLA2 are also used in combination with OKT3 to treat chronic or acute inflammation associated with kidney transplant. Also generally for treating symptoms secondary to renal dysfunction including sepsis, cell membrane damage secondary to organ failure and tissue rejection following kidney transplant. sPLA2 in combination with erythropoetin is used to stimulate red cell production in a mammal.

The sPLA2 inhibitors are known from e.g. US5654326 and EP95302166.4.

ADVANTAGE - Prior art methods treat the cause of the renal dysfunction and not, e.g. the build up of fluids or cell membrane damage. Administration of sPLA2 inhibitors does not prevent the underlying causes of renal dysfunction but the symptoms will be reduced in severity or extent. Combination therapies allow standard treatment to be supplemented with the administration of sPLA2 inhibitors.

☐ 48. Document ID: WO 200121587 A2 EP 1220839 A2 AU 200070537 A

L3: Entry 48 of 58 File: DWPI Mar 29, 2001

DERWENT-ACC-NO: 2001-300001
DERWENT-WEEK: 200253

TITLE: New indole derivatives are inhibitors of sPLA2, useful for treating inflammatory diseases

INVENTOR: HARPER, R W; LIN, H ; RICHETT, M E

PRIORITY-DATA: 1999US-154836P (September 20, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200121587 A2	March 29, 2001	E	117	C07D209/00
EP 1220839 A2	July 10, 2002	E	000	C07D209/22
AU 200070537 A	April 24, 2001		000	C07D209/00

INT-CL (IPC): A61 K 31/404; A61 P 29/00; C07 D 209/00; C07 D 209/22

ABSTRACTED-PUB-NO: WO 200121587A
BASIC-ABSTRACT:

NOVELTY - Indole derivatives (I) are new.

DETAILED DESCRIPTION - Indole derivatives of formula (I) and their salts, solvates and prodrugs, are new:

R1 = 7-20C alkyl, 7-20C haloalkyl, 7-20C alkenyl, 7-20C alkynyl, carbocyclic radical or heterocyclic radical, all optionally substituted with 1 or more non-interfering substituents; or is (L1)-R11;

R11 = 7-20C alkyl, 7-20C haloalkyl, 7-20C alkenyl, 7-20C alkynyl, carbocyclic radical or heterocyclic radical, all optionally substituted with 1 or more non-interfering substituents;

L1 = a divalent linking group of 1-8 atoms;

R2 = H or a group comprising 1-4 non-hydrogen atoms plus any required hydrogen atoms;

R3 = -(L3)-Z;

L3 = a bond, -CH2-, O, S, -NH or -C(=O)-;

Z = -C(=NORa)-C(=X)-NH2, -C(=X)-C(=O)NH2, or C(Ra)(Ra)-C(=X)-NH2;

X = O or S;

Ra = H, 1-8C alkyl, aryl, 1-8C alkaryl, 1-8C alkoxy, aralkyl or CN;

R4 = (Lh) (hydroxyfunctional amide);

Lh = an hydroxyfunctional amide linker of length 1-8 (sic);

R5 = H, a non-interfering substituent or -(La)-(acidic group);

La = an acidic linker of length 1-8 (sic);

R6, R7 = H; a non-interfering substituent; or a carbocyclic or heterocyclic radical both optionally substituted with non-interfering substituents.

ACTIVITY - Antiinflammatory.

MECHANISM OF ACTION - Human non-pancreatic secretory phospholipase A2 (sPLA2) inhibitors.

In a test to determine inhibition of sPLA2, 2-((3 (aminooxoacetal)-2-ethyl--1-(phenylmethyl)-1H-indol-4-yl)oxy)-N (hydroxy)acetamide had IC50 18.7 plus or minus 3 nM.

USE - For inhibiting sPLA2 mediated release of fatty acids, and treating inflammatory diseases, e.g. inflammatory bowel disease, septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis, rheumatoid arthritis and osteoarthritis.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Clip Img | Image
KWIC | Draw Desc

☐ 49. Document ID: EP 1081135 A2

L3: Entry 49 of 58 File: DWPI Mar 7, 2001

DERWENT-ACC-NO: 2001-246796
DERWENT-WEEK: 200249

TITLE: New indole-3-glyoxylamide derivatives are useful as nonpancreatic secretory phospholipase A2 inhibitors, e.g. for treatment of septic shock, pancreatitis, trauma, asthma, allergic rhinitis and arthritis

INVENTOR: BACH, N J; DILLARD, R D ; DRAHEIM, S E

PRIORITY-DATA: 1994US-0221916 (April 1, 1994)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1081135 A2	March 7, 2001	E	088	C07D209/22

INT-CL (IPC): A61 K 31/404; A61 P 43/00; C07 D 209/22

ABSTRACTED-PUB-NO: EP 1081135A
BASIC-ABSTRACT:

NOVELTY - New indole-3-glyoxylamide derivatives are claimed.

DETAILED DESCRIPTION - The new indole-3-glyoxylamide derivatives are of formula (I).

X = O or S;

R1 = R or L-R;

R = 7-20C alkyl, 7-20C alkenyl, 7-20C alkynyl or a carbocylic or heterocyclic group, all optionally substituted with non-interfering substituents;

L = linking group of 1-12 atoms selected from C and H only, S only, O only, N and H only, C, H and S only, and C, H and O only;

R2 = H, halogen, 1-3C alkyl, 3-4C cycloalkyl, 3-4C cycloalkenyl, 1-2C alkoxy, 1-2C alkylthio or a non-interfering substituent having 1-3 atoms other than H;

R4, R5 = H, non-interfering substituents or La-A, at least one being La-A;

La = acid linked having an acid linker length of 1-4 (sic);

A = acidic group;

R6, R7 = H, non-interfering substituents, or carbocyclic or heterocyclic groups optionally substituted with non-interfering substituents.

An INDEPENDENT CLAIM is included for a pharmaceutical formulation comprising (I) for inhibiting sPLA2-mediated release of fatty acids, especially in the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis and rheumatoid arthritis

ACTIVITY - Antiinflammatory;

Antiallergic.

MECHANISM OF ACTION - Inhibitor of nonpancreatic secretory phospholipase A2 (sPLA2). 2-(3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-benzyl-1H-indol-4-ylo- xy)acetic acid had an IC50 of 9 nM against human sPLA2 in the assay described in Anal. Biochem., 204, 190 (1992).

USE - (I) are sPLA2 inhibitors useful for inhibiting sPLA2-mediated release of fatty acids, especially in the treatment of septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis and rheumatoid arthritis.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Clip Img | Image

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☐ 50. Document ID: JP 2002522386 W WO 200007591 A1 AU 9953314 A EP 1100493 A1

L3: Entry 50 of 58 File: DWPI Jul 23, 2002

DERWENT-ACC-NO: 2000-195442
DERWENT-WEEK: 200263

TITLE: New acylsulfonamide indole compounds inhibit human non-pancreatic secretory phospholipase A2-mediated fatty acid release to treat inflammatory diseases

INVENTOR: MIHELICH, E D; PHILLIPS, M L ; WARSHAWSKY, A M

PRIORITY-DATA: 1998US-095109P (August 3, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2002522386 W	July 23, 2002		062	C07D209/22
WO 200007591 A1	February 17, 2000	E	070	A61K031/335
AU 9953314 A	February 28, 2000		000	A61K031/335
EP 1100493 A1	May 23, 2001	E	000	A61K031/335

INT-CL (IPC): A61 K 31/335; A61 K 31/38; A61 K 31/395; A61 K 31/40; A61 K 31/405; A61 K 31/41; A61 K 31/415; A61 K 31/42 ; A61 K 31/425; A61 K 31/435; A61 K 31/44; A61 K 31/445; A61 K 31/47; A61 K 31/495; A61 K 31/505; A61 K 31/535; A61 P 1/18; A61 P 7/00; A61 P 9/10; A61 P 11/00; A61 P 19/02; A61 P 19/06; A61 P 27/16; A61 P 29/00; A61 P 31/04; A61 P 35/00; A61 P 37/08; A61 P 43/00; C07 D 205/02; C07 D 209/04; C07 D 209/12 ; C07 D 209/14; C07 D 209/22; C07 D 209/82; C07 D 211/26; C07 D 211/30; C07 D 211/86; C07 D 213/36; C07 D 213/50; C07 D 213/56; C07 D 215/12; C07 D 219/12; C07 D 231/12; C07 D 231/54; C07 D 231/56; C07 D 233/54; C07 D 233/56; C07 D 233/58; C07 D 237/30; C07 D 239/26; C07 D 241/04; C07 D 241/42; C07 D 249/04; C07 D 249/08; C07 D 251/22; C07 D 261/08; C07 D 263/32; C07 D 275/02; C07 D 277/02; C07 D 285/04; C07 D 285/06; C07 D 285/08; C07 D 285/10; C07 D 285/12; C07 D 317/26; C07 D 317/28; C07 D 319/12; C07 D 401/04; C07 D 401/06; C07 D 401/12; C07 D 401/14; C07 D 403/04; C07 D 403/06; C07 D 403/12; C07 D 403/14; C07 D 405/04; C07 D 405/06; C07 D 405/12; C07 D 405/14; C07 D 409/04; C07 D 409/06; C07 D 409/12; C07 D 409/14; C07 D 413/04; C07 D 413/06; C07 D 413/12; C07 D 413/14; C07 D 417/04; C07 D 417/06; C07 D 417/12; C07 D 417/14; C07 D 473/00

ABSTRACTED-PUB-NO: WO 200007591A
BASIC-ABSTRACT:

NOVELTY - Acylsulfonamide indole compounds and their pharmaceutically acceptable salts, solvates or prodrug derivatives are new.

DETAILED DESCRIPTION - The indole compounds are of formula (I).

R1 = 7-20C alkyl, 7-20C haloalkyl, 7-20C alkenyl, 7-20C alkynyl, carbocycle or heterocycle (optionally substituted by one or more non-interfering substituents) or (L1)-R11;

R2 = H or group containing 1-4 non-H atoms;

R3 = (L3)-Z;

L1 = 1-8 atom linking group;

R11 = 7-20C alkyl, 7-20C haloalkyl, 7-20C alkenyl, 7-20C alkynyl, carbocycle or heterocycle (optionally substituted by one or more non-interfering substituents);

L3 = divalent linker chosen from bond, CH2, O, S, NH or C(O);

Z = acetamide, thioacetamide, glycoxylamide, thioglyoxylamide, hydrazide, thiohydrazide, -C(R31)(R32)C(=X)NH2, -C(=X)C(=X)NH2 or -C(R31)(R32)C(=X)NHNH2;

R31, R32 = H, 1-8C alkyl, 1-8C haloalkyl or 3-4C cycloalkyl;

X = O or S;

R4, R5 = H, non-interfering substituent or (La)-(acylsulfonamide);

La = 1-8 atom divalent acid linker, provided that at least one of R4 and R5 = (La)-(acylsulfonamide) group; and

R6, R7 = H, non-interfering substituent, carbocycle (optionally substituted by non-interfering substituent) or heterocycle (optionally substituted by non-interfering substituent).

An INDEPENDENT CLAIM is also included for compounds of formula (II).

Formula (II),

R16 = H, 1-8C alkyl, aryl, 1-8C alkaryl, 1-8C alkoxy, aralkyl or halo;

R44 = methyl, ethyl, phenyl or CF3;

L4 = OCH2, SCH2, -(N(R40)CH2)-, -(C(R40)(R42)C(R41)(R43))- or -(OC(CH3))-;

R40-R43 = H or 1-8C alkyl;

R22 = H, methyl, ethyl, propyl, isopropyl, cyclopropyl, F, CF3, Cl, Br or OCH3;

R13 = 1-8C alkyl, 1-8C alkoxy, phenyl, halophenyl, S-(1-8C) alkyl, 1-8C haloalkyl, 1-8C hydroxyalkyl or halo; and

t = 0-5.

ACTIVITY - Anti-inflammatory.

MECHANISM OF ACTION - Human non-pancreatic secretory phospholipase A2 (sPLA2)-mediated fatty acid release inhibitor. Test compounds were assayed for sPLA2 inhibition by a known method Analytical Biochemistry 1992; 204:190-197. All compounds were tested in triplicate, typically at final concentrations of 5 mu g/ml. IC50 values for human secreted phospholipase A2 inhibition in 5 compounds were as follows (mu M): 12, 7, 17, 9 and 16. The results showed that the compounds were useful in inhibiting sPLA2.

USE - (I) are used to treat mammals including humans to alleviate the pathological effects of inflammatory diseases (claimed) including septic shock, inflammatory bowel disease, sepsis, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, asthma, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute and chronic bronchitis, acute and chronic bronchiolitis, osteoarthritis, gout, spondyloarthropathies, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enteropathic spondylitis, juvenile arthropathy, juvenile ankylosing spondylitis, reactive arthropathy, infectious or post-infectious arthritis, gonococcal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with 'vasculitic syndromes', polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgic rheumatica, joint cell arteritis, calcium channel deposition arthropathies, pseudo-gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis, Henoch-Schonlein purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathies, hyperlipoproteinemia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial mediterranean fever, Behat's disease, systemic lupus erythematosus, relapsing polychondritis, and related disease.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Clip Img | Image

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☐ 51. Document ID: WO 200007590 A1 EP 1100492 A1 JP 2002522385 W US 6451839 B1

L3: Entry 51 of 58 File: DWPI Feb 17, 2000

DERWENT-ACC-NO: 2000-195441
DERWENT-WEEK: 200271

TITLE: New indole compounds are human non-pancreatic secretory phospholipase A2-mediated fatty acid release inhibitors used to treat inflammatory diseases e.g. septic shock, inflammatory bowel disease and pancreatitis.

INVENTOR: BACH, N J; DILLARD, R D ; DRAHEIM, S E ; MIHELICH, E D ; SUAREZ, T

PRIORITY-DATA: 1998US-095114P (August 3, 1998), 2001US-0762069 (January 30, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200007590 A1	February 17, 2000	E	077	A61K031/335
EP 1100492 A1	May 23, 2001	E	000	A61K031/335
JP 2002522385 W	July 23, 2002		068	C07D209/40
US 6451839 B1	September 17, 2002		000	A61K031/404

INT-CL (IPC): A61 K 31/335; A61 K 31/34; A61 K 31/35; A61 K 31/38; A61 K 31/39; A61 K 31/395; A61 K 31/40; A61 K 31/404 ; A61 K 31/41; A61 K 31/415; A61 K 31/42; A61 K 31/425; A61 K 31/435; A61 K 31/44; A61 K 31/445; A61 K 31/47; A61 K 31/495; A61 K 31/505; A61 K 31/52; A61 K 31/535; A61 P 1/18; A61 P 5/14; A61 P 5/18; A61 P 9/00; A61 P 11/00; A61 P 11/06; A61 P 11/08; A61 P 17/06; A61 P 19/00; A61 P 19/02; A61 P 29/00; A61 P 31/04; A61 P 31/12; A61 P 37/08; A61 P 43/00; C07 D 205/02; C07 D 207/08; C07 D 207/36; C07 D 209/04 ; C07 D 209/12; C07 D 209/14; C07 D 209/40; C07 D 209/82; C07 D 211/26; C07 D 211/30; C07 D 211/86; C07 D 213/36; C07 D 213/50; C07 D 213/56; C07 D 215/12; C07 D 219/12; C07 D 231/12; C07 D 231/54; C07 D 231/56; C07 D

233/54; C07 D 233/56; C07 D 233/58; C07 D 237/30; C07 D 239/26; C07 D 241/04; C07 D 241/42; C07 D 249/04; C07 D 249/08; C07 D 251/22; C07 D 261/08; C07 D 263/32; C07 D 275/02; C07 D 277/02; C07 D 285/04; C07 D 285/06; C07 D 285/08; C07 D 285/10; C07 D 285/12; C07 D 307/38; C07 D 307/52; C07 D 309/32; C07 D 317/26; C07 D 317/28; C07 D 319/12; C07 D 327/06; C07 D 401/04; C07 D 401/06; C07 D 401/12; C07 D 401/14; C07 D 403/04; C07 D 403/06; C07 D 403/12; C07 D 403/14; C07 D 405/04; C07 D 405/06; C07 D 405/12; C07 D 405/14

ABSTRACTED-PUB-NO: WO 200007590A
BASIC-ABSTRACT:

NOVELTY - Indole compounds (I) and their pharmaceutically acceptable salts, solvates or prodrug derivatives are new.

DETAILED DESCRIPTION - Indole compounds of formula (I) and their pharmaceutically acceptable salts, solvates or prodrug derivatives are new.

R1 = 7-20C alkyl, 7-20C haloalkyl, 7-20C alkenyl, 7-20C alkynyl, carbocycle or heterocycle (optionally substituted by one or more non-interfering substituents) or (L1)-R11;

R2 = H or group containing 1-4 non-H atoms;

R3 = (L3)-Z';

L1 = 1-8 atom linking group;

R11 = 7-20C alkyl, 7-20C haloalkyl, 7-20C alkenyl, 7-20C alkynyl, carbocycle or heterocycle (optionally substituted by one or more non-interfering substituents);

L3 = divalent linker chosen from a bond, CH2, O, S, NH or C(O);

Z' = NHC(=X)Y, F, Cl, Br or I;

X = O or S;

Y = NH2, 1-4C alkyl, CF3, CONH2 or CH2Z;

R4, R5 = H, non-interfering substituent or (La)-acidic group;

La = 1-8 atom divalent acid linker, provided that at least one of R4 and R5 = (La)-acidic group; and

R6, R7 = H, non-interfering substituent or carbocycle or heterocycle (both optionally substituted by non-interfering substituent).

An INDEPENDENT CLAIM is also included for compounds of formula (II).

R16 = H, 1-8C alkyl, aryl, 1-8C alkaryl, 1-8C alkoxy, aralkyl or halo;

L4 = OCH2, SCH2, -(N(R40)CH2)-, -(C(R40)(R42)C(R41)(R43))- or -(OC(CH3))-;

R40-R43 = H or 1-8C alkyl;

R22 = H, methyl, ethyl, propyl, isopropyl, cyclopropyl, F, CF3, Cl, Br or OCH3;

R13 = 1-8C alkyl, 1-8C alkoxy, phenyl, halophenyl, S-(1-8C) alkyl, 1-8C haloalkyl, 1-8C hydroxyalkyl or halo; and

t = 0-5.

ACTIVITY - Anti-inflammatory; Antiarthritic; Antirheumatic; Osteopathic.

MECHANISM OF ACTION - Human non-pancreatic secretory phospholipase A2 (sPLA2)-mediated fatty acid release inhibitor.

Test compounds were assayed for sPLA2 inhibition by a known method Analytical Biochemistry 1992; 204:190-197. All compounds were tested in triplicate, typically at final concentrations of 5 mu g/ml. IC50 values for human secreted phospholipase A2 inhibition in 9 compounds were as follows (mu M): 0.049, 65, 51, 45, 6.8, 13, 0.021, 0.074 and 0.017. The results showed that the compounds were useful in inhibiting sPLA2.

USE - (I) are used to treat mammals including humans to alleviate the pathological effects of inflammatory diseases (claimed) including septic shock, inflammatory bowel disease, sepsis, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, asthma, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute and chronic

bronchitis, acute and chronic bronchiolitis, osteoarthritis, gout, spondyloarthropathies, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enteropathic spondylitis, juvenile arthropathy, juvenile ankylosing spondylitis, reactive arthropathy, infectious or post-infectious arthritis, gonococcal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with 'vasculitic syndromes', polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgic rheumatica, joint cell arteritis, calcium channel deposition arthropathies, pseudo-gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing), miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis, Henoch-Schonlein purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathies, hyperlipoproteinemia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's disease, systemic lupus erythematosus, relapsing polychondritis, and related disease.

☐ 52. Document ID: WO 200000201 A1 JP 2002519325 W AU 9947106 A EP 1091738 A1 US 6384041 B1

L3: Entry 52 of 58 File: DWPI Jan 6, 2000

DERWENT-ACC-NO: 2000-137025
DERWENT-WEEK: 200246

TITLE: New pyrrolo(2,3-d)pyrimidines useful for treating mammalian inflammatory diseases

INVENTOR: HUTCHISON, D R; MARTINELLI, M J ; WILSON, T M

PRIORITY-DATA: 1998US-091248P (June 30, 1998), 2000US-0719318 (December 11, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200000201 A1	January 6, 2000	E	112	A61K031/505
JP 2002519325 W	July 2, 2002		116	C07D487/04
AU 9947106 A	January 17, 2000		000	A61K031/505
EP 1091738 A1	April 18, 2001	E	000	A61K031/505
US 6384041 B1	May 7, 2002		000	A61K031/505

INT-CL (IPC): A61 K 31/505; A61 K 31/519; A61 K 31/535; A61 K 31/675; A61 P 5/18; A61 P 11/06; A61 P 19/00; A61 P 19/02 ; A61 P 29/00; A61 P 43/00; C07 D 413/12; C07 D 487/04; C07 F 9/02

ABSTRACTED-PUB-NO: US 6384041B
BASIC-ABSTRACT:

NOVELTY - Pyrrolo(2,3-d)pyrimidines, their pharmaceutical salts and prodrugs, useful for treating mammalian inflammatory diseases, are new.

DETAILED DESCRIPTION - Pyrrolo(2,3-d)pyrimidines (I), their pharmaceutical salts and prodrugs are new where:

R2 = hydrogen (H), a non-interfering group, a carbocylcic group optionally substituted with one or more non-interfering substituents or a heterocyclic group optionally substituted with one or more non-interfering groups;

R4 = L4-acid group;

L4 = 1-4 membered divalent acid linker;

R5 = L5Z;

L5 = a bond, CH2, -O-,-S-,1-NH- or -C=O-;

Z = (II), (III) or (IV);

R51, R52 = H, 1-8Calkyl, 1-8C haloalkyl, 3-4C cycloalkyl;

X = oxygen (O) or sulfur (S); R6=H or a group with 1-4 non-hydrogen atoms having any number of required hydrogen atoms;

R7 = (a), (b) or (c);

(a) = 7-20C alkyl, 7-20C haloalkyl, 7-20C alkynyl; carbocyclic radical or heterocyclic radical;

(b) = (a) optionally substituted with one or more non-interfering groups;

(c) = L7R71;

L7 = groups consisting of (carbon (C) and H only), (S only), (O only), (nitrogen (N) and H only), (C, H and S only) or (C, H and O only); and

R71 = (a) or (b)

. An INDEPENDENT CLAIM is made for pharmaceutical compositions comprising (I).

ACTIVITY - Anti-inflammatory.

MECHANISM OF ACTION - Human non-pancreatic secretory phospholipase A2 (sPLA2) inhibitor.

USE - Useful for treating or preventing inflammatory diseases in mammals, especially those associated with sPLA2 e.g. inflammatory bowel disease, septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis, rheumatoid arthritis and osteoarthritis. (I) are also useful for inhibiting sPLA2 mediated release of fatty acids.

ADVANTAGE - Additional compounds are available for treating diseases associated with sPLA2.
ABSTRACTED-PUB-NO:

WO 200000201A EQUIVALENT-ABSTRACTS:

NOVELTY - Pyrrolo(2,3-d)pyrimidines, their pharmaceutical salts and prodrugs, useful for treating mammalian inflammatory diseases, are new.

DETAILED DESCRIPTION - Pyrrolo(2,3-d)pyrimidines (I), their pharmaceutical salts and prodrugs are new where:

R2 = hydrogen (H), a non-interfering group, a carbocylcic group optionally substituted with one or more non-interfering substituents or a heterocyclic group optionally substituted with one or more non-interfering groups;

R4 = L4-acid group;

L4 = 1-4 membered divalent acid linker;

R5 = L5Z;

L5 = a bond, CH2, -O-,-S-,1-NH- or -C=O-;

Z = (II), (III) or (IV);

R51, R52 = H, 1-8Calkyl, 1-8C haloalkyl, 3-4C cycloalkyl;

X = oxygen (O) or sulfur (S); R6=H or a group with 1-4 non-hydrogen atoms having any number of required hydrogen atoms;

R7 = (a), (b) or (c);

(a) = 7-20C alkyl, 7-20C haloalkyl, 7-20C alkynyl; carbocyclic radical or heterocyclic radical;

(b) = (a) optionally substituted with one or more non-interfering groups;

(c) = L7R71;

L7 = groups consisting of (carbon (C) and H only), (S only), (O only), (nitrogen (N) and H only), (C, H and S only) or (C, H and O only); and

R71 = (a) or (b)

. An INDEPENDENT CLAIM is made for pharmaceutical compositions comprising (I).

ACTIVITY - Anti-inflammatory.

MECHANISM OF ACTION - Human non-pancreatic secretory phospholipase A2 (sPLA2) inhibitor.

USE - Useful for treating or preventing inflammatory diseases in mammals, especially those associated with sPLA2 e.g. inflammatory bowel disease, septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis, rheumatoid arthritis and osteoarthritis. (I) are also useful for inhibiting sPLA2 mediated release of fatty acids.

ADVANTAGE - Additional compounds are available for treating diseases associated with sPLA2.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 53. Document ID: WO 9925340 A1 JP 2001522884 W AU 9914073 A EP 1043991 A1

L3: Entry 53 of 58 File: DWPI May 27, 1999

DERWENT-ACC-NO: 1999-357548
DERWENT-WEEK: 200204
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TITLE: Method for treating Alzheimer's disease with phospholipase A2 inhibitor

INVENTOR: WATANABE, A M

PRIORITY-DATA: 1997US-066035P (November 14, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9925340 A1	May 27, 1999	E	096	A61K031/40
JP 2001522884 W	November 20, 2001		093	A61K045/00
AU 9914073 A	June 7, 1999		000	A61K031/40
EP 1043991 A1	October 18, 2000	E	000	A61K031/40

INT-CL (IPC): A61 K 31/40; A61 K 31/403; A61 K 31/436; A61 K 31/4365; A61 K 31/437; A61 K 45/00; A61 P 25/28; A61 P 43/00; C07 D 209/88; C07 D 471/04; C07 D 491/052; C07 D 495/04

ABSTRACTED-PUB-NO: WO 9925340A
BASIC-ABSTRACT:

NOVELTY - Treating Alzheimer's disease comprises administration of a substituted tricyclic type human non-pancreatic secretory phospholipase A2 (sPLA2) inhibitor.

ACTIVITY - None Given.

MECHANISM OF ACTION - sPLA2 inhibitor.

USE - The method is useful for preventing or treating Alzheimer's disease.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc
Clip Img | Image

☐ 54. Document ID: US 6436983 B1 WO 9925339 A1 AU 9914058 A EP 1039901 A1 JP 2001522883 W

L3: Entry 54 of 58 File: DWPI Aug 20, 2002

DERWENT-ACC-NO: 1999-347394
DERWENT-WEEK: 200257
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TITLE: Treating Alzheimer's disease comprises administration of human non pancreatic secretory phospholipase A2 (sPLA2) inhibitor

INVENTOR: WATANABE, A M

PRIORITY-DATA: 1997US-066036P (November 14, 1997), 2000US-0529247 (April 10, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 6436983 B1	August 20, 2002		000	A61K031/40
WO 9925339 A1	May 27, 1999	E	056	A61K031/40
AU 9914058 A	June 7, 1999		000	
EP 1039901 A1	October 4, 2000	E	000	A61K031/40
JP 2001522883 W	November 20, 2001		057	A61K031/404

INT-CL (IPC): A61 K 31/40; A61 K 31/404; A61 K 31/405; A61 P 25/28

ABSTRACTED-PUB-NO: US 6436983B
BASIC-ABSTRACT:

NOVELTY - Treating Alzheimer's disease comprises administration of a 1H-indole-3-glyoxylamide type human non pancreatic secretory phospholipase A2 (sPLA2) inhibitor.

ACTIVITY - None given.

MECHANISM OF ACTION - sPLA2 inhibitor.

USE - Useful for preventing or treating Alzheimer's disease.
ABSTRACTED-PUB-NO:

WO 9925339A EQUIVALENT-ABSTRACTS:

NOVELTY - Treating Alzheimer's disease comprises administration of a 1H-indole-3-glyoxylamide type human non pancreatic secretory phospholipase A2 (sPLA2) inhibitor.

ACTIVITY - None given.

MECHANISM OF ACTION - sPLA2 inhibitor.

USE - Useful for preventing or treating Alzheimer's disease.

☐ 55. Document ID: WO 9921546 A1 JP 2001520991 W AU 9912798 A EP 1030661 A1 US 6274616 B1

L3: Entry 55 of 58 File: DWPI May 6, 1999

DERWENT-ACC-NO: 1999-312858
DERWENT-WEEK: 200203

TITLE: New 1H-indole-3-glycoxylamide derivative useful as a human non-pancreatic secretory phospholipase A2 inhibitor pro-drug

INVENTOR: DENNEY, M L; MORIN, J M ; SALL, D J ; SAWYER, J S

PRIORITY-DATA: 1997US-063280P (October 27, 1997), 2000US-0509754 (March 29, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9921546 A1	May 6, 1999	E	028	A61K031/21
JP 2001520991 W	November 6, 2001		027	A61K031/404
AU 9912798 A	May 17, 1999		000	
EP 1030661 A1	August 30, 2000	E	000	A61K031/21
US 6274616 B1	August 14, 2001		000	A61K031/40

INT-CL (IPC): A61 K 31/21; A61 K 31/24; A61 K 31/40; A61 K 31/404; A61 K 31/405; A61 P 1/18; A61 P 5/18; A61 P 7/00; A61 P 7/06; A61 P 9/00; A61 P 9/02; A61 P 11/00; A61 P 11/06; A61 P 17/02; A61 P 19/00; A61 P 19/02; A61 P 19/06; A61 P 27/16; A61 P 29/00; A61 P 37/08; A61 P 43/00; C07 C 69/608; C07 C 69/612; C07 C 69/616 ; C07 C 69/618; C07 C 69/73; C07 C 229/32; C07 C 229/34; C07 D 209/12; C07 D 209/14; C07 D 209/18

ABSTRACTED-PUB-NO: US 6274616B
BASIC-ABSTRACT:

NOVELTY - ((3-(2-Amino-1,2-dioxoethyl)-1-((1,1'-biphenyl)-3-ylmethyl)-2-methyl-1H-indol-4-yl)oxy)acetic acid N,N-diethylglycolamido ester (I) is a new human non-pancreatic secretory phospholipase A2 inhibitor pro-drug.

DETAILED DESCRIPTION - ((3-(2-Amino-1,2-dioxoethyl)-1-((1,1'-biphenyl)-3-ylmethyl)-2-methyl-1H-indol-4-yl)oxy)acetic acid N,N-diethylglycolamido ester (I) is a new human non-pancreatic secretory phospholipase A2 inhibitor pro-drug.

An INDEPENDENT CLAIM is made for applying (I) as a method to inhibit human non-pancreatic sensory phospholipase A2 (sPLA2) mediated release of fatty acids.

ACTIVITY - None given.

MECHANISM OF ACTION - sPLA2 inhibitor pro-drug.

USE - Used for the prophylaxis and treatment of mammalian and human disorders induced or maintained by the overproduction of sPLA2 (e.g. septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis, hemophilia, cystic fibrosis and rheumatoid arthritis).

ADVANTAGE - The compound can be given orally with better bioavailability compared to other esterified pro-drugs. Fischer 344 rats were fasted overnight before being given a single oral dose of sPLA2 inhibitor in acacia (10 %). The dose was 10 mg/kg of parent acid (5 ml/kg). Two rats per compound were used in a comparison between morpholino-N-ethyl ester (I) and the following esters: methyl (A), ethyl (B), pivalate (C) isopropyl (D) and N,N-diethylglycolamido (E). Blood samples were taken at 0.5, 1, 2, 4, 8 and 24 hours to determine blood concentrations using high performance liquid chromatography. The maximum blood concentrations (ng/ml) for (I) and (A) - (E) were 1163, 201, 56, 98, 491 and 751. The corresponding areas under the plasma concentration-time curves (for an 8 hour period) were 5192, 1129, 241, 361, 2570 and 3398.
ABSTRACTED-PUB-NO:

WO 9921546A EQUIVALENT-ABSTRACTS:

NOVELTY - ((3-(2-Amino-1,2-dioxoethyl)-1-((1,1'-biphenyl)-3-ylmethyl)-2-methyl-1H-indol-4-yl)oxy)acetic acid N,N-diethylglycolamido ester (I) is a new human non-pancreatic secretory phospholipase A2 inhibitor pro-drug.

DETAILED DESCRIPTION - ((3-(2-Amino-1,2-dioxoethyl)-1-((1,1'-biphenyl)-3-ylmethyl)-2-methyl-1H-indol-4-yl)oxy)acetic acid N,N-diethylglycolamido ester (I) is a new human non-pancreatic secretory phospholipase A2 inhibitor pro-drug.

An INDEPENDENT CLAIM is made for applying (I) as a method to inhibit human non-pancreatic sensory phospholipase A2 (sPLA2) mediated release of fatty acids.

ACTIVITY - None given.

MECHANISM OF ACTION - sPLA2 inhibitor pro-drug.

USE - Used for the prophylaxis and treatment of mammalian and human disorders induced or maintained by the overproduction of sPLA2 (e.g. septic shock, adult respiratory distress syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis, hemophilia, cystic fibrosis and rheumatoid arthritis).

ADVANTAGE - The compound can be given orally with better bioavailability compared to other esterified pro-drugs. Fischer 344 rats were fasted overnight before being given a single oral

dose of sPLA2 inhibitor in acacia (10 %). The dose was 10 mg/kg of parent acid (5 ml/kg). Two rats per compound were used in a comparison between morpholino-N-ethyl ester (I) and the following esters: methyl (A), ethyl (B), pivalate (C) isopropyl (D) and N,N-diethylglycolamido (E). Blood samples were taken at 0.5, 1, 2, 4, 8 and 24 hours to determine blood concentrations using high performance liquid chromatography. The maximum blood concentrations (ng/ml) for (I) and (A) - (E) were 1163, 201, 56, 98, 491 and 751. The corresponding areas under the plasma concentration-time curves (for an 8 hour period) were 5192, 1129, 241, 361, 2570 and 3398.

☐ 56. Document ID: DE 69714289 E WO 9824756 A1 AU 9855892 A EP 946495 A1 BR 9713987 A HU 9904172 A2 MX 9905112 A1 JP 2001505575 W KR 2000069248 A US 6353128 B1 EP 946495 B1

L3: Entry 56 of 58 File: DWPI Aug 29, 2002

DERWENT-ACC-NO: 1998-377225
DERWENT-WEEK: 200264

TITLE: Treating sPLA2 in mammals - by administering new and known phenyl:acetamide derivatives, used to treat septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock etc.

INVENTOR: HARPER, R W; HERRON, D K ; JUNIOR, T G ; GOODSON, T

PRIORITY-DATA: 1996US-032508P (December 3, 1996), 1997US-0976858 (November 24, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
DE 69714289 E	August 29, 2002		000	C07C235/34
WO 9824756 A1	June 11, 1998	E	050	C07C229/00
AU 9855892 A	June 29, 1998		000	
EP 946495 A1	October 6, 1999	E	000	
BR 9713987 A	February 8, 2000		000	C07C229/00
HU 9904172 A2	May 28, 2000		000	C07C229/00
MX 9905112 A1	October 1, 1999		000	C07C229/00
JP 2001505575 W	April 24, 2001		044	C07C233/11
KR 2000069248 A	November 25, 2000		000	C07C233/05
US 6353128 B1	March 5, 2002		000	C07C229/00
EP 946495 B1	July 24, 2002	E	000	C07C235/34

INT-CL (IPC): A61 K 31/16; A61 K 31/165; A61 K 31/192; A61 P 3/00; C07 C 229/00; C07 C 233/05; C07 C 233/11; C07 C 235/34; C07 C 303/00

ABSTRACTED-PUB-NO: EP 946495B
BASIC-ABSTRACT:

Inhibiting sPLA2 in a mammal comprises administering a compound of formula (I) or its salt, racemate or optical isomer: R1 = H or O(CH2)nZ; R2 = H or OH; R3, R4 = H, halo or 1-4C alkyl; one of R5 and R6 = YR7 and the other = H; Y = O or CH2; R7 = phenyl (optionally substituted by 1 or 2 halo, 1-4C alkyl, 1-4C alkoxy or phenyl (optionally substituted by 1 or 2 halo)); Z = CO2R, PO3R2 or SO3R; R = H or 1-4C alkyl; and n = 1-8.

(I), its salt, racemate or optical isomer are new provided that (i) when R6 = YR7, R1 = H; (ii) when R1-R4, R6 = H, R5 = YR7 and Y = O, R7 cannot be phenyl; and (iii) when R1-R4, R6 = H, R5 = YR7 and Y = CH2, R7 cannot be phenyl substituted by one methoxy or two Cl.

USE - (I) are sPLA2 inhibitors useful in alleviating the pathological effects of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis by inhibiting sPLA2-mediated release of fatty acid, thus inhibiting or preventing the arachidonic acid cascade and its deleterious products in mammal, including humans (claimed).

Administration may be oral, by aerosol, rectal, transdermal, subcutaneous, intravenous,

intramuscular or intranasal. Typical daily dosage is 0.01-50 mg/kg/day. Unit doses may contain 0.1-1000 mg of active ingredient.
ABSTRACTED-PUB-NO:

US 6353128B EQUIVALENT-ABSTRACTS:

Inhibiting sPLA2 in a mammal comprises administering a compound of formula (I) or its salt, racemate or optical isomer: R1 = H or O(CH2)nZ; R2 = H or OH; R3, R4 = H, halo or 1-4C alkyl; one of R5 and R6 = YR7 and the other = H; Y = O or CH2; R7 = phenyl (optionally substituted by 1 or 2 halo, 1-4C alkyl, 1-4C alkoxy or phenyl (optionally substituted by 1 or 2 halo)); Z = CO2R, PO3R2 or SO3R; R = H or 1-4C alkyl; and n = 1-8.

(I), its salt, racemate or optical isomer are new provided that (i) when R6 = YR7, R1 = H; (ii) when R1-R4, R6 = H, R5 = YR7 and Y = O, R7 cannot be phenyl; and (iii) when R1-R4, R6 = H, R5 = YR7 and Y = CH2, R7 cannot be phenyl substituted by one methoxy or two Cl.

USE - (I) are sPLA2 inhibitors useful in alleviating the pathological effects of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis by inhibiting sPLA2-mediated release of fatty acid, thus inhibiting or preventing the arachidonic acid cascade and its deleterious products in mammal, including humans (claimed).

Administration may be oral, by aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal. Typical daily dosage is 0.01-50 mg/kg/day. Unit doses may contain 0.1-1000 mg of active ingredient.

Inhibiting sPLA2 in a mammal comprises administering a compound of formula (I) or its salt, racemate or optical isomer: R1 = H or O(CH2)nZ; R2 = H or OH; R3, R4 = H, halo or 1-4C alkyl; one of R5 and R6 = YR7 and the other = H; Y = O or CH2; R7 = phenyl (optionally substituted by 1 or 2 halo, 1-4C alkyl, 1-4C alkoxy or phenyl (optionally substituted by 1 or 2 halo)); Z = CO2R, PO3R2 or SO3R; R = H or 1-4C alkyl; and n = 1-8.

(I), its salt, racemate or optical isomer are new provided that (i) when R6 = YR7, R1 = H; (ii) when R1-R4, R6 = H, R5 = YR7 and Y = O, R7 cannot be phenyl; and (iii) when R1-R4, R6 = H, R5 = YR7 and Y = CH2, R7 cannot be phenyl substituted by one methoxy or two Cl.

USE - (I) are sPLA2 inhibitors useful in alleviating the pathological effects of septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis and rheumatoid arthritis by inhibiting sPLA2-mediated release of fatty acid, thus inhibiting or preventing the arachidonic acid cascade and its deleterious products in mammal, including humans (claimed).

Administration may be oral, by aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal. Typical daily dosage is 0.01-50 mg/kg/day. Unit doses may contain 0.1-1000 mg of active ingredient.

WO 9824756A

☐ 57. Document ID: EP 846687 A1 JP 2002515053 W WO 9824437 A1 AU 9853655 A ZA 9710878 A US 5972972 A BR 9713993 A MX 9905167 A1 KR 2000057366 A HU 200000292 A2 EP 846687 B1 DE 69706027 E TW 432051 A ES 2160897 T3

L3: Entry 57 of 58 File: DWPI Jun 10, 1998

DERWENT-ACC-NO: 1998-299930
DERWENT-WEEK: 200236

TITLE: New pyrazole derivatives used to treat e.g. septic shock - are human non-pancreatic secretory phospholipase A2 inhibitors, and inhibit mediated release of fatty acids and arachidonic acid cascade

INVENTOR: DOMAN, P J; HITE, G A ; MIHELICH, E D ; SUAREZ, T ; WILLETTS, S E ; MICHELICH, E D

PRIORITY-DATA: 1996US-033216P (December 4, 1996), 1997US-0984261 (December 3, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 846687 A1	June 10, 1998	E	044	C07D231/44
JP 2002515053 W	May 21, 2002		068	C07D231/44
WO 9824437 A1	June 11, 1998	E	000	A61K031/495
AU 9853655 A	June 29, 1998		000	A61K031/495
ZA 9710878 A	August 31, 1999		078	C07D000/00
US 5972972 A	October 26, 1999		000	C07D401/04
BR 9713993 A	February 8, 2000		000	A61K031/495
MX 9905167 A1	October 1, 1999		000	A61K031/495
KR 2000057366 A	September 15, 2000		000	C07D231/00
HU 200000292 A2	April 28, 2001		000	A61K031/495
EP 846687 B1	August 8, 2001	E	000	C07D231/44
DE 69706027 E	September 13, 2001		000	C07D231/44
TW 432051 A	May 1, 2001		000	C07D231/44
ES 2160897 T3	November 16, 2001		000	C07D231/44

INT-CL (IPC): A61 K 31/395; A61 K 31/415; A61 K 31/44; A61 K 31/4439; A61 K 31/47; A61 K 31/4725; A61 K 31/495; A61 K 31/497; A61 K 31/50; A61 P 1/18; A61 P 7/06; A61 P 9/02; A61 P 11/06; A61 P 11/16; A61 P 19/02; A61 P 27/16; A61 P 29/00; A61 P 37/00; A61 P 37/08; A61 P 43/00; C07 D 0/00; C07 D 231/00; C07 D 231/44; C07 D 231/52; C07 D 401/00; C07 D 401/04; C07 D 401/14; C07 D 403/00; C07 D 403/04; C07 D 405/00; C07 D 405/14; C07 D 409/00; C07 D 409/12; C07 D 409/14; C07 D 417/00; C07 D 417/14; C07 D 213:00; C07 D 401/04; C07 D 213:00; C07 D 401/04; C07 D 213:00; C07 D 401/04

ABSTRACTED-PUB-NO: EP 846687A
BASIC-ABSTRACT:

Pyrazole derivatives of formula (I) and their salts are new: R1 = Ph, isoquinolin-3-yl, pyrazinyl, pyridin-2-yl (optionally 4-substituted by 1-4C alkyl, 1-4C alkoxy, CN or (CH2)nCONH2; n = 0-2; R2 = Ph (optionally substituted by 1-3 1-4C alkyl, CN, halo, NO2, CO2(1-4C) alkyl or CF3), naphthyl or thiophene (optionally substituted by 1-3 halo); R3 = H, Ph, phenyl(2-6C) alkenyl, pyridyl, naphthyl, quinolinyl, 1-4C alkylthioazolyl or Ph (optionally substituted by 1-2 1-4C alkyl, CN, CONH2, NO2, CF3, halo, 1-4C alkoxy, CO2(1-4C) alkyl, OPh or SR4 or by one O(CH2)pR5, Ph or OR6, or by two substituents which form methylene dioxy; R4 = 1-4C alkyl or halophenyl; p = 1-3; R5 = CN, COOH, CONH2 or tetrazolyl; R6 = cyclopentyl, cyclohexenyl or Ph (substituted by halo or 1-4C alkoxy); and m = 1-5.

USE - (I) are human non-pancreatic secretory phospholipase A2 inhibitors (sPLA2) and are useful for alleviating the pathological effects of septic shock, adult respiratory syndrome (ARDS), pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathies, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infections arthritis, gonoccocal arthritis, Tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with vasculitic syndrome, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgia, rheumatica, joint cell arteritis, calcium crystal deposition arthropathies, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis, carpal tunnel syndrome, repetitive use injury, miscellaneous forms of arthritis, neuropathic joint disease, haemarthrosis, Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentre reticulohistocytosis, arthritis associated with certain diseases, surcoilosis, haemochromatosis, sickle cell disease and other haemoglobinopathies, hyperlipoproteinaemia, hypogammaglobulinaemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's disease, systemic lupus erythematosis or relapsing polychondritis (claimed). (I) inhibit sPLA2 mediated release of fatty acids and inhibits or prevents arachidonic acid cascade and its deleterious products.
ABSTRACTED-PUB-NO:

EP 846687B EQUIVALENT-ABSTRACTS:

Pyrazole derivatives of formula (I) and their salts are new: R1 = Ph, isoquinolin-3-yl, pyrazinyl, pyridin-2-yl (optionally 4-substituted by 1-4C alkyl, 1-4C alkoxy, CN or (CH2)nCONH2; n = 0-2; R2 = Ph (optionally substituted by 1-3 1-4C alkyl, CN, halo, NO2, CO2(1-4C) alkyl or CF3), naphthyl or thiophene (optionally substituted by 1-3 halo); R3 = H, Ph, phenyl(2-6C) alkenyl, pyridyl, naphthyl, quinolinyl, 1-4C alkylthioazolyl or Ph (optionally substituted by 1-2 1-4C alkyl, CN, CONH2, NO2, CF3, halo, 1-4C alkoxy, CO2(1-4C) alkyl, OPh or SR4 or by one O(CH2)pR5, Ph or OR6, or by two substituents which form methylene dioxy; R4 = 1-4C alkyl or halophenyl; p = 1-3; R5 = CN, COOH, CONH2 or tetrazolyl; R6 = cyclopentyl,

cyclohexenyl or Ph (substituted by halo or 1-4C alkoxy); and m = 1-5.

USE - (I) are human non-pancreatic secretory phospholipase A2 inhibitors (sPLA2) and are useful for alleviating the pathological effects of septic shock, adult respiratory syndrome (ARDS), pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathies, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infections arthritis, gonoccocal arthritis, Tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with vasculitic syndrome, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgia, rheumatica, joint cell arteritis, calcium crystal deposition arthropathies, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis, carpal tunnel syndrome, repetitive use injury, miscellaneous forms of arthritis, neuropathic joint disease, haemarthrosis, Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentre reticulohistocytosis, arthritis associated with certain diseases, surcoilosis, haemochromatosis, sickle cell disease and other haemoglobinopathies, hyperlipoproteinaemia, hypogammaglobulinaemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's disease, systemic lupus erythematosis or relapsing polychondritis (claimed). (I) inhibit sPLA2 mediated release of fatty acids and inhibits or prevents arachidonic acid cascade and its deleterious products.

US 5972972A

Pyrazole derivatives of formula (I) and their salts are new: R1 = Ph, isoquinolin-3-yl, pyrazinyl, pyridin-2-yl (optionally 4-substituted by 1-4C alkyl, 1-4C alkoxy, CN or (CH2)nCONH2; n = 0-2; R2 = Ph (optionally substituted by 1-3 1-4C alkyl, CN, halo, NO2, CO2(1-4C) alkyl or CF3), naphthyl or thiophene (optionally substituted by 1-3 halo); R3 = H, Ph, phenyl(2-6C) alkenyl, pyridyl, naphthyl, quinolinyl, 1-4C alkylthioazolyl or Ph (optionally substituted by 1-2 1-4C alkyl, CN, CONH2, NO2, CF3, halo, 1-4C alkoxy, CO2(1-4C) alkyl, OPh or SR4 or by one O(CH2)pR5, Ph or OR6, or by two substituents which form methylene dioxy; R4 = 1-4C alkyl or halophenyl; p = 1-3; R5 = CN, COOH, CONH2 or tetrazolyl; R6 = cyclopentyl, cyclohexenyl or Ph (substituted by halo or 1-4C alkoxy); and m = 1-5.

USE - (I) are human non-pancreatic secretory phospholipase A2 inhibitors (sPLA2) and are useful for alleviating the pathological effects of septic shock, adult respiratory syndrome (ARDS), pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathies, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infections arthritis, gonoccocal arthritis, Tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with vasculitic syndrome, polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgia, rheumatica, joint cell arteritis, calcium crystal deposition arthropathies, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis, carpal tunnel syndrome, repetitive use injury, miscellaneous forms of arthritis, neuropathic joint disease, haemarthrosis, Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentre reticulohistocytosis, arthritis associated with certain diseases, surcoilosis, haemochromatosis, sickle cell disease and other haemoglobinopathies, hyperlipoproteinaemia, hypogammaglobulinaemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's disease, systemic lupus erythematosis or relapsing polychondritis (claimed). (I) inhibit sPLA2 mediated release of fatty acids and inhibits or prevents arachidonic acid cascade and its deleterious products.

☐ 58. Document ID: WO 8901773 A JP 3054092 B2 AU 8824249 A EP 395653 A US 5019508 A JP 04506447 W CA 1335800 C EP 395653 B1 DE 3855080 G US 5552530 A JP 09208492 A JP 2872256 B2 JP 2000102399 A

L3: Entry 58 of 58 File: DWPI Mar 9, 1989

DERWENT-ACC-NO: 1989-085394
DERWENT-WEEK: 200033

TITLE: Mammalian synovial phospholipase A2 - used in food processing, design and screening of inflammation inhibitors, as an anticancer drug or vaccine adjuvant etc

INVENTOR: JOHNSON, L K; PRUZANSKI, W ; SEILHAMER, J J ; VADAS, P

PRIORITY-DATA: 1988US-0231865 (August 16, 1988), 1987US-0089883 (August 27, 1987), 1988US-0215726 (July 6, 1988), 1990US-0579263 (September 4, 1990), 1991US-0750230 (August 19, 1991), 1993US-0058988 (May 5, 1993), 1994US-0283793 (August 1, 1994)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 8901773 A	March 9, 1989	E	070	
JP 3054092 B2	June 19, 2000		026	A61K039/395
AU 8824249 A	March 31, 1989		000	
EP 395653 A	November 7, 1990		000	
US 5019508 A	May 28, 1991		026	
JP 04506447 W	November 12, 1992		020	C12N009/16
CA 1335800 C	June 6, 1995		000	C12N015/55
EP 395653 B1	March 6, 1996	E	033	A61K009/20
DE 3855080 G	April 11, 1996		000	A61K009/20
US 5552530 A	September 3, 1996		031	C07K016/18
JP 09208492 A	August 12, 1997		026	A61K039/395
JP 2872256 B2	March 17, 1999		029	C12N015/09
JP 2000102399 A	April 11, 2000		026	C12Q001/34

INT-CL (IPC): A61 K 9/20; A61 K 37/54; A61 K 38/00; A61 K 38/46; A61 K 39/39; A61 K 39/395; A61 K 47/42; A61 P 29/00; C07 H 15/12; C07 K 14/00; C07 K 16/18; C07 K 16/40; C12 N 5/20; C12 N 9/16; C12 N 9/20; C12 N 15/00; C12 N 15/09; C12 N 15/55; C12 P 21/08; C12 Q 1/00; C12 Q 1/34; C12 Q 1/44; G01 N 33/50; G01 N 33/531; G01 N 33/573

ABSTRACTED-PUB-NO: EP 395653B
BASIC-ABSTRACT:

Compsn. is claimed comprising double-stranded DNA constructs contg. a heterologous region comprising a coding sequence for a mammalian synovial phospholipase A2 (sPLA2), the compsn. being free of constructs not contg. the heterologous region.

Also claimed is a compsn. comprising mammalian sPLA2 free of contaminating proteins and a compsn. comprising antibodies recognising an epitope unique to a mammalian sPLA2.

USE - The pure sPLA2 compsns. can be used in food processing and to delay the onset of rancidity in fish. They are partic. useful as a tool in the design and screening of inflammation inhibitors. They may also be useful as an anti-cancer drug. The purified sPLA2 can also be used as an adjuvant in activity of sPLA2, e.g. to treat inflammatory disorders, endotoxic shock or respiratory distress. PLA2 antagonists, such as sPLA2 muteins could also be used in place of antibodies. The antibodies can also be used in the purification of sPLA2 or in diagnostic applications.
ABSTRACTED-PUB-NO:

US 5019508A EQUIVALENT-ABSTRACTS:

A composition comprising a double-stranded DNA construct containing a heterologous region comprising a coding sequence for a mammalian synovial phospholipase A2 (sPLA2) comprising the amino acid sequence GTKFLSYKFSNSGSRITC, said composition being substantially free of constructs not containing said heterologous region.

A compsn. consists of a double-stranded DNA construct contg. a heterologous region comprising a coding sequence, pref. the amino acid sequence of the pre-enzyme, for a, pref. human, mammalian synovial phospholipase A2(SPA). The SPA is pref. a mutein where the amino acid residue corresp. to His48 in the native mammalian SPA is replaced by an amino acid residue other than His, esp. Glu or Asp. The DNA construct also contains a replicon, esp. a bacterial plasmid, yeast plasmid, bacteriophage or chromosome.

USE - As important tool in the design of anti-inflammatory drugs. (26pp)

US 5552530A

A composition comprising purified polyclonal antibodies that specifically bind to an epitope located in the region of amino acids 67-85 of human synovial phospholipase A2 Type A and inhibit the phospholipase activity of the synovial phospholipase A2.